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ORIGINAL CONTRIBUTIONS

Volume 22 **August, 1955** Number 8

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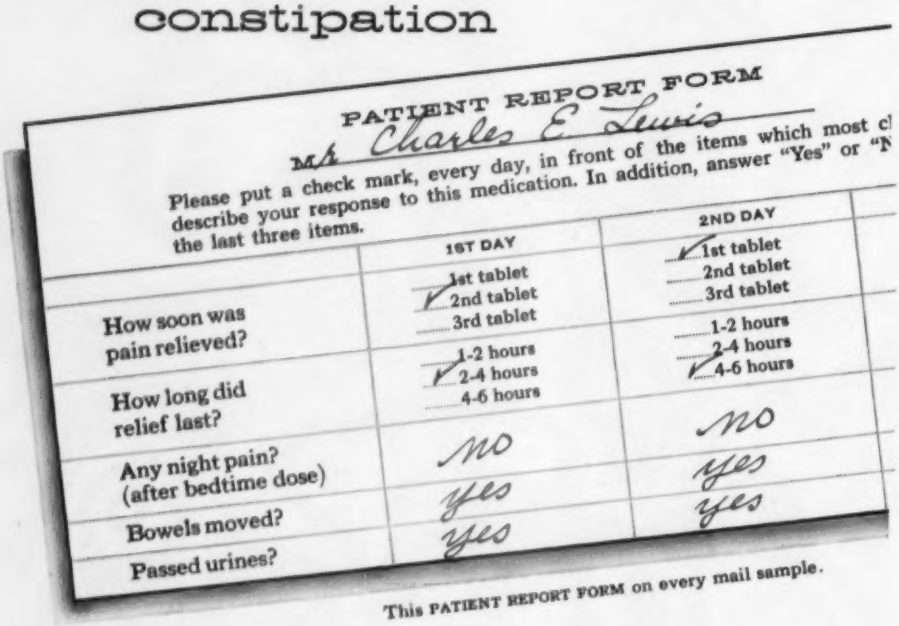

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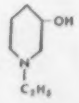

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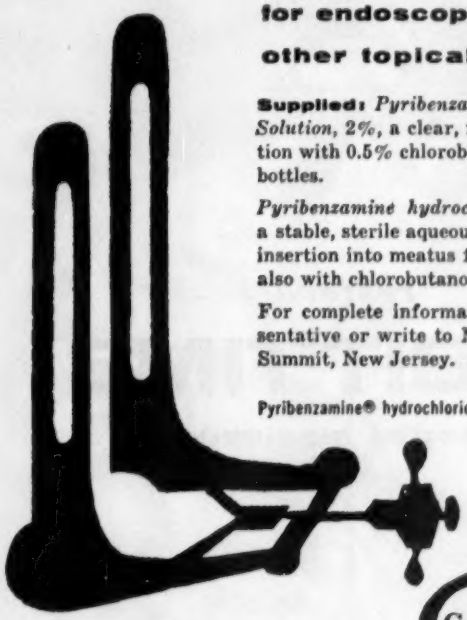

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Business and Editorial Office:
229 WEST BERRY STREET
SUITE 302-310
FORT WAYNE, INDIANA

Printing Office:
117 E. MAIN ST.
BERNE, INDIANA

Advertising Office:
VINING & MEYERS
35 EAST WACKER DRIVE
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Published Monthly at 117 East Main St., Berne, Ind.

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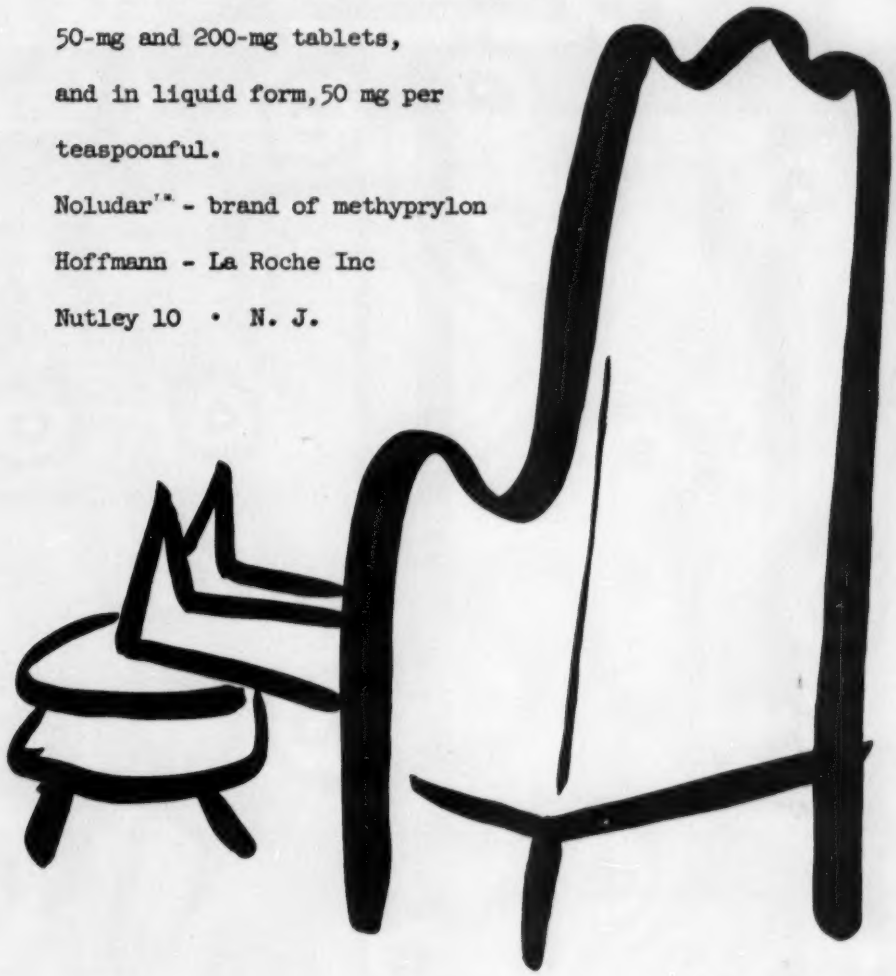

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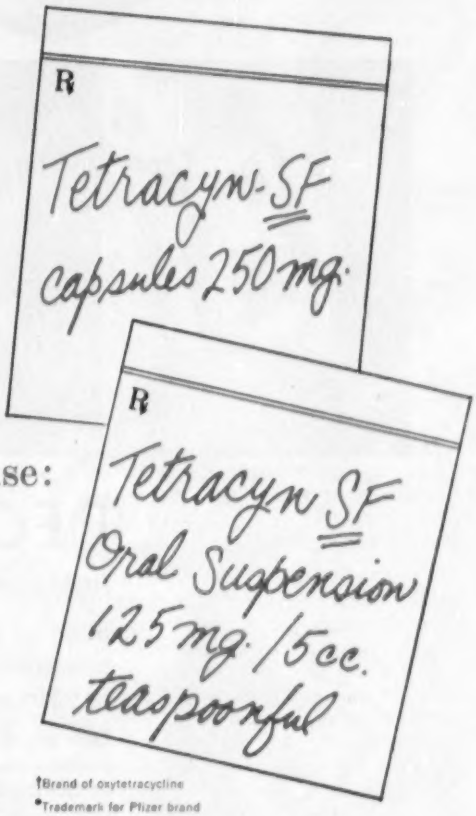

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1. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared in Collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Washington, D. C., 1952. 2. Martí-Ibáñez, F.: Antibiotic Med. *1*:247 (May) 1955. 3. Dumas, K. J.; Carlozzi, M., and Wright, W. A.: Antibiotic Med. *1*:296 (May) 1955. 4. Milberg, M. B., and Michael, M., Jr.: Ann. New York Acad. Sc., In press. 5. Prigot, A.: Ibid.

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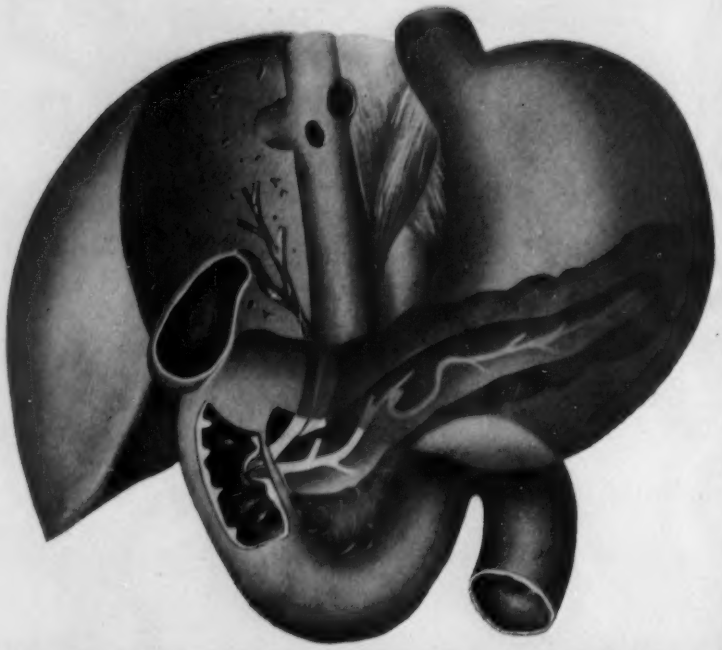

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THE EFFECT OF DIET IN THE BLOOD PRESSURE AND HEART RATE OF NORMAL DOGS. ANIMAL FAT

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(With the technical assistance of G. B. Green)

IN PREVIOUS studies (1) it was shown that when diets high in carbohydrate (cracker meal or boiled rice) or in protein (horse meat) were fed to animals following a prolonged fast, there was no essential difference in the effect on blood pressure and heart rate when the diets were fed at a low maintenance level of intake (60 cal/M^2/hr/24 hrs) which stopped weight loss but allowed no gain. However, when these diets were fed at the luxus consumption level of intake (twice the low maintenance level) which resulted in a progressive gain in weight, a marked difference was found. The diets high in carbohydrate caused a marked and highly significant elevation of systolic pressure and heart rate, but the diastolic pressure was normal or low; the diets high in protein resulted in a low systolic pressure with a slower heart rate. Since the curves for increasing body weight were practically the same on the two diets, differences in weight gain were not responsible for the different effects on blood pressure and heart rate. When the high carbohydrate diets were fed to a fasting animal and the characteristic circulatory effects established, substitution of an isocaloric high protein diet, caused a prompt lowering of systolic pressure and heart rate to the protein level. It was found that the preliminary fast was necessary to obtain a permanent effect of the high carbohydrate diet, since without it the effect passed off in slightly over two weeks even though the diet was continued. In a further study (2), the value of the capillary resistance and the level of the circulating eosinophiles were used as joint indices of the approximate degree of activity of the pituitary-adrenal cortical system. It was found that fasting increased the level of activity of this system and that luxus consumption diets high in carbohydrate tended to maintain the fasting level. Isocaloric diets high in protein had an opposite and antagonistic action.

In the above studies the animals were fasted until the blood pressure declined to the "stable fasting value" before the diets were given. The reasons for the preliminary fast were:—(1) The "stable fasting value" is the true minimal nutritional level of blood pressure and since it is very similar in the same animal during repeated fasts it gives a more constant control base line. (2) Fasting reduces the "momentum" of the metabolic mill and may thus prevent masking of true food effects due to momentum (vide infra). (3) Fasting is an alarming stimulus (10) and sensitizes the animal to other alarming stimuli and may thus help to demonstrate potential, specific food effects which might remain latent without this sensitization.

Departments of Physiology and Pharmacology and Surgery, The Creighton University School of Medicine, Omaha, Nebraska.

Submitted Mar. 4, 1955.

The effects of the high carbohydrate or protein diets terminated when the diets were stopped and there were no after effects. Hence, the behavior of the blood pressure during fasting and the value on the control kennel diet or on balanced high calory diets were normal even after two years of severe dietary stress consisting of repeated, prolonged fasting and realimentation with diets high in carbohydrate or protein (1,3).

The present paper describes experiments in which diets high in animal fat were studied in a similar manner.

Methods

Six trained, standardized dogs, three males and three females were used. All had been used in the experiments on carbohydrate and protein (1) but four had borne the brunt of these experiments (Dogs I to IV). Following these previous studies the animals were placed on the routine kennel diet (Nutrena) and rested for four months during which blood pressure was determined on six days each week. Before starting the experiments with fat it was definitely established that the control blood pressure and the response to fasting were normal.

In the present experiments, each high fat diet was given after a prolonged fast. The preliminary fast and the subsequent period on the high fat diet will be referred to as a "fat episode." The general plan was to study the blood pressure and heart rate while the animals were receiving the high fat diet and also to determine whether there were accumulative effects from repeated "fat episodes." In some experiments the preliminary fast for the next "fat episode" began immediately after the high fat diet of the preceding episode, while in others, the animals were placed on the kennel diet for from 35 to 51 days at the end of the fat episode, hence, the preliminary fast for the next episode began from the kennel diet.

The Diets. Beef suet alone or combined with unsalted butter were used as animal fats. A 30 percent solution of Difco Beef Extract was used to flavor and moisten the diets. In most experiments, the preliminary fast was terminated by giving the animal only suet flavored and homogenized with beef extract in a Waring blender. Some animals would eat this voraciously for prolonged periods, while others would eat it for only a few days. Following this preliminary "saturation" with fat, suet, butter or a combination of both were mixed with cracker meal or horse meat. All diets contained 50 percent or more of the calories from fat and the total caloric intake was usually at the luxus consumption level of 120 cal/M^2/hr/24 hrs. Most animals ate these diets fairly readily but if they refused, immediate changes were made in the composition of the diet but the fat was always kept at 50 percent or more of the total calories. A tablespoon or more of Brewers yeast

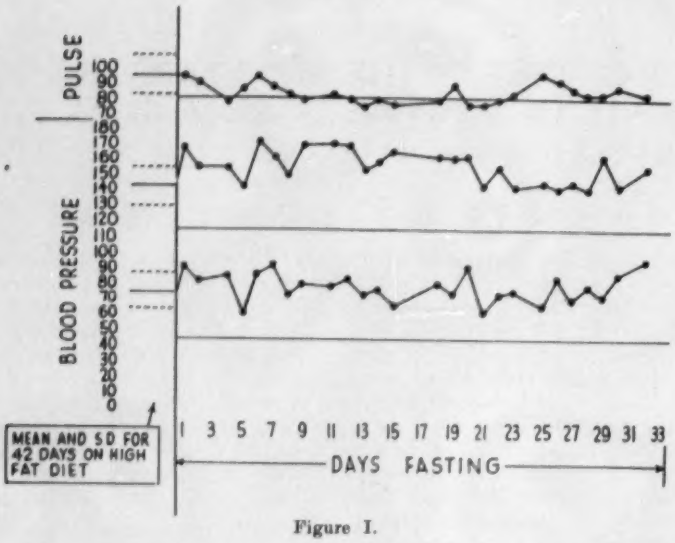

Figure I.

Dog. I. Fast after second fat episode in 1950. Base lines are control values on kennel diet before experiment with fat.

was mixed with the diet and one multicebrin[2] tablet was given daily to supply vitamins.

In the early experiments the fat was mixed indiscriminately with horse meat or cracker meal and changes were often made during a fat episode. However, it soon appeared that fat and cracker meal gave the most striking effects and in later experiments this was the mixture most frequently used.

Since the main purpose was to combine high fat diets and the stress of fasting, a fat episode was often interrupted by a short fast and then continued. These fasts were often too short to be statistically significant but the fasts starting and/or terminating each fat episode were sufficiently long to be of statistical significance.

The diets were fed at approximately 3:00 P.M. and the blood pressure and heart rates were determined between 6:00 and 11:00 A.M., a set time being used for each dog. The pressure was often determined again in the afternoon.

Throughout the entire experimental period of slightly over two years, blood pressure was determined six days weekly using the auscultatory method of Allen (5) with certain modifications (6,7). The mean of from 10 to 15 consecutive readings was considered as the blood pressure for that day.

Total white blood cell and eosinophile counts were made daily at 11:00 A.M. The eosinophile counts were made in a Spencer Bright line hemocytometer using the diluting fluid of Manners (4). The control counts had been made during a two month period after the experiments with carbohydrate and protein but just before the experiments with fat.

The majority of the experiments were done on four dogs and of these, three were subjected to six fat episodes with six major fasts while one was subjected to two fat episodes and four fasts in 1950 and six of each during 1952-54. Two additional dogs were subjected to only two fat episodes and four fasts.

The duration of the high fat diets varied from 13 to 42 days, the majority being over 30 days, the duration of the diets was determined either by the willingness of the animal to continue the diet or the advent of illness.

RESULTS

(A) *Complications.*

Liver function was frequently determined with bromsulphthalein and all dogs at times showed abnormal retention and on a few occasions retention reached 30 to 40% (normal 2% or less). High retention often diminished spontaneously while the high fat diets were continued. Three dogs became acutely ill with anorexia, vomiting and jaundice. Administration of crystalline vitamin B_{12} followed by a high meat diet resulted in prompt recovery.

One dog had a severe generalized convulsion (blood sugar 149 mg/ percent).

Tarry stools were sometimes seen in the early period of realimentation.

With the above exceptions, the animals remained in good condition.

(B) *The First Experiment With Fat in 1950.*

A Pilot experiment was done on one dog in 1950 and since the results were very striking, this experiment will be described in detail.

A trained standardized dog that had never been knowingly subjected to dietary stress was fasted after being on the kennel diet for several months. The effect of fasting on the blood pressure and heart rate was normal (dotted curve in Fig. II). The period of high fat diet following this fast lasted 20 days and a short fast immediately afterward was nearly normal. Following this, the blood pressure on the kennel diet and a subsequent (3rd Fast) were normal. The second period of high fat diet following the third fast lasted for 42 days. During the first 20 days the animal ate 127

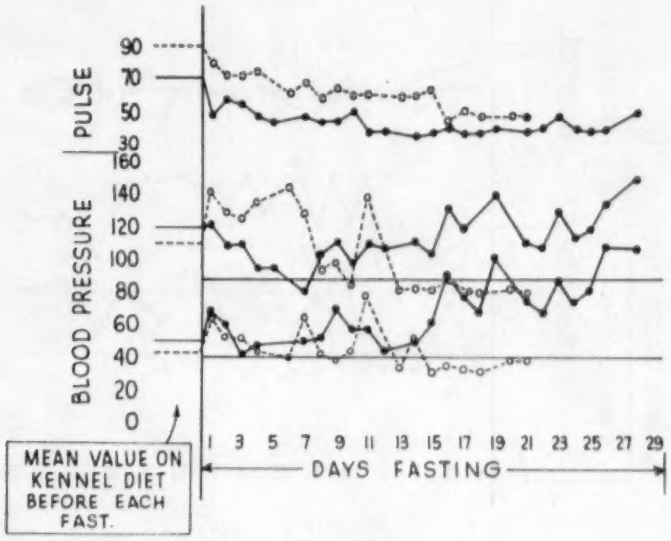

Figure II.

Dog. I.

o . . . o Fast from kennel diet in 1950 just before beginning experiments with fat.

. ——— . Fast from kennel diet after sixth fat episode in 1953. Base lines are mean stable fasting values for 4 fasts before experiments with fat.

gms. of suet mixed with beef extract daily. The suet was then mixed with cracker meal or meat for 22 days more. The blood pressure, especially the diastolic, was very significantly elevated above the normal value during this period of high fat diet. The fast which followed this (4th Fast) was extremely abnormal in that the pressure showed no tendency to decline to the stable fasting value during 32 days of fasting, in fact, it remained significantly above the control pressure on kennel diet while the heart rate was the same as the control value (Fig. I). The fast was terminated because of excessive and dangerous loss of weight. During the next 24 days on kennel diet the blood pressure, especially the systolic, remained very high. A 55 day fast from the kennel diet was still abnormal. The animal was then placed on a luxus consumption diet of horse meat and the pressure gradually became normal as was the 6th Fast. The animal was then used in the experiments on protein and carbohydrate (1) and reacted similarly to other animals.

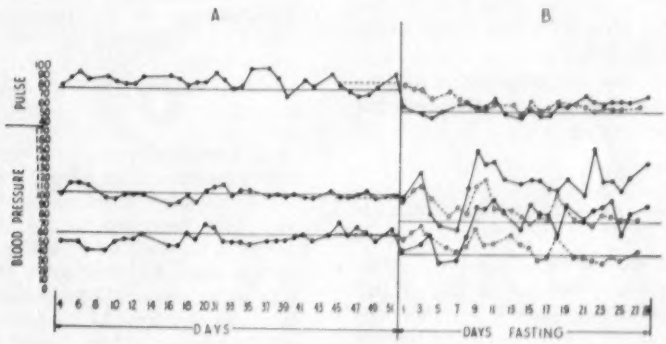

Figure III.

Dog II..

(A)

. ——— . Blood pressure and pulse rate on kennel diet for 51 days after fourth fat episode. Base lines are values on kennel diet established before starting experiments with fat.

(B)

o . . . o Fast from kennel diet after experiments with protein and carbohydrate and just before beginning experiments with fat.

. ——— . Fast from kennel diet after fourth fat episode. Base lines are mean stable fasting values for 4 fasts before experiments with fat.

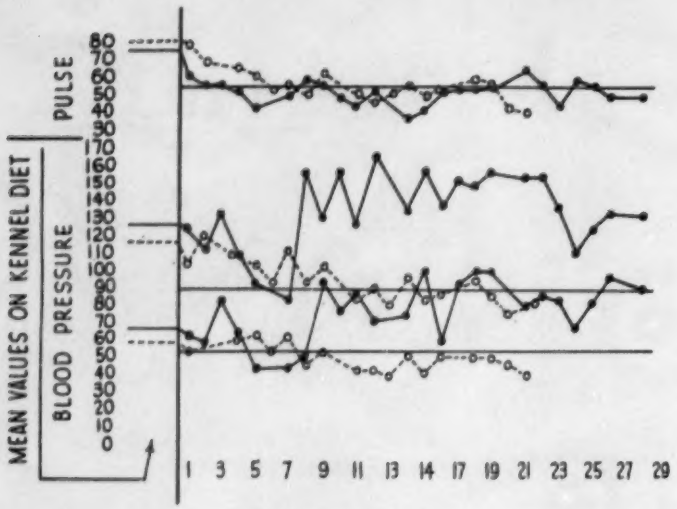

Figure IV.

Dog IV.

o . . . o Fast from kennel diet after experiments with protein and carbohydrate and just before beginning experiments with fat.

. ——— . Fast from kennel diet for 51 days after fourth fat episode. Base lines are mean stable fasting values for 6 fasts before experiments with fat.

This experiment illustrated the following points:— (1) That the effects of fat episodes may be accumulative, in this case developing after the second one; (2) that the blood pressure on the high fat diet may be very high; (3) that after two episodes the blood pressure may remain high during a prolonged fast.

In reviewing this experiment it was decided that the abnormality of the 4th Fast (Fig. I) may have been due to momentum of the metabolic mill (1) since the blood pressure was very high during the period on high fat diet just preceding the fast. If this were true, then the effect would not be specific for fat but similar, although more pronounced, than the effect of any luxus consumption diet preceding a fast (6).

Experiments with fat were discontinued until the studies on protein and carbohydrate were finished but were resumed in 1952-54 using six dogs.

(C) *Fat Experiments 1952-54.*

I *The Blood Pressure on a High Fat Diet Administered after a Fast.*

The level of the blood pressure was not predictable, it could be higher, lower or the same as the control value. In 26 experiments on four dogs it was not significantly elevated in 14; was elevated in 11 and normal in 1. Furthermore, it varied in the same dog during different fat episodes. The reasons for these variations are not known but may be due to some type of irregularly occurring depletion due to the prolonged preliminary fast and the abnormality of the high fat diet.

II *The Effect of Fat Episodes on the Blood Pressure During a Succeeding Fast.*

In previous studies on fasting (6) it was shown that the behavior of the blood pressure during fasting can be divided into two stages. The *first stage* is the descent to the Stable Fasting Value and *second stage* is the Stable Fasting Value. The first stage is greatly influenced by the previous nutritional level, being prolonged and characterized by wide fluctuations when this has been at the luxus consumption level, but short and with few fluctuations when it has been at the low maintenance level. The stage of the stable fasting value is independent of the previous nutritional level and is surprisingly constant in repeated fasts on the same animal. It is obvious from these facts that in order to be comparable, fasts should always start from the same diet and nutritional level. In this laboratory there has been established for each dog a weighed amount of Nutrena which maintains optimal weight and the control blood pressure level. All strictly comparable fasts begin from this diet.

As previously stated, it seemed possible that in the first experiment on Dog I in 1950, the failure of the blood pressure to decrease during fasting (Fig. I) may have been due to the high calory content of the previous fat diet. In 1952 this experiment was repeated on the same dog, but after the fat episode the animal was placed on the kennel diet for 51 days before the fast was started. As seen in Fig. II, even after this prolonged period on kennel diet the blood pressure during fasting was abnormal. The systolic and diastolic pressures first decreased and reached the stable fasting values on the 7th and 4th days respectively, but from then until the 29th day there was an irregular but progressive elevation of both and they did not decline to the stable fasting values. This is in striking contrast to the fast beginning from the kennel diet with no preceding fat episode (Fig. II, dotted curve). It is interesting to note that the pulse was slightly slower during the abnormal fast than during the normal one.

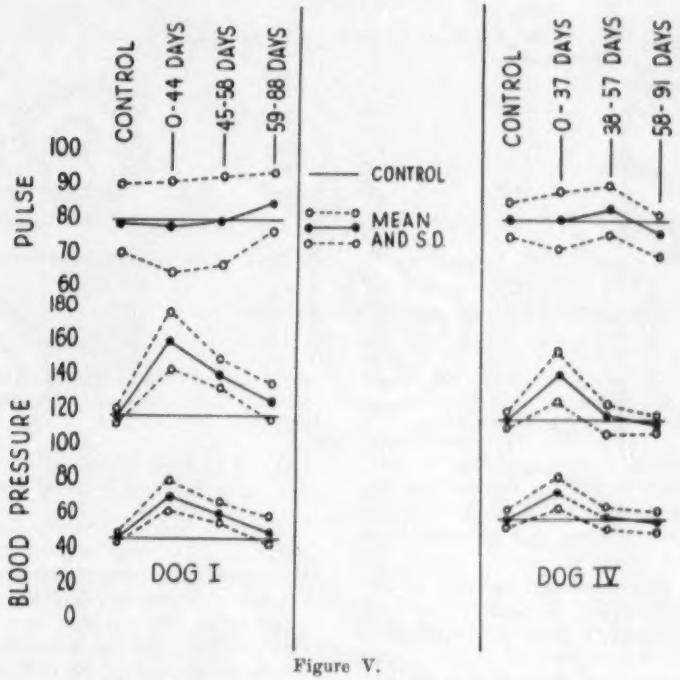

Figure V.

Shows "Momentum of the Metabolic Mill" as it influences blood pressure. After six fat episodes the animals were placed on a balanced high calory diet for 90 days and the blood pressure was very high (Table I), they were then placed on the kennel diet without an intervening fast. Base lines represent the mean control values on kennel diet as repeatedly established before the experiments with fat.

Fig. III shows a complete experiment on Dog III. After the 4th fat episode the animal was placed on the kennel diet for 51 days. As shown in (A) the blood pressure and heart rate on the kennel diet were very stable and the mean values (100/55-85) were the same as the mean control values obtained on four different occasions on kennel diet. The systolic and diastolic pressure both fell during the early part of the fast (B) and reached the stable fasting levels. Following the fall, there was an explosive rise of both and during 28 days of fasting the values remained far above the usual stable fasting values. This is strikingly different from the blood pressure during a fast which started from the kennel diet not preceded by fat episodes (dotted curve). The pulse rates were not strikingly different during the two fasts. The normal fast was done after the experiments with protein and carbohydrate were completed and just before the experiments with fat were started. The abnormal fast was after the 4th fat episode.

Figure IV shows an experiment on Dog IV in which the animal was placed on the kennel diet for 51 days after the 4th fat episode. The pressure on the kennel diet was only slightly above the usual control value. During the first seven days of the fast the systolic and diastolic pressures descended to the stable fasting values but this was quickly followed by a spectacular rise of both and the usual stable fasting values were not attained. In the control fast from the kennel diet without preceding fat episodes (dotted curve), the pressures quickly reached the usual stable fasting values. Pulse rates were not essentially different during the two fasts.

Comparable results were obtained on a fourth dog.

Two other dogs were subjected to two fat episodes each and placed on the kennel diet after both. Both fasts were normal in one dog while the second fast showed some abnormality in the other dog. Since the effects of several fat episodes are accumulative it was concluded that two were not sufficient to produce abnormal responses in these two dogs.

These experiments show that after several fat episodes, changes occurred in the homeostatic mechanisms regulating blood pressure. If the animal was receiving the usual optimal kennel diet and therefore not subjected to any dietary stress, the blood pressure was normal, but if the animal was subjected to the stress of fasting the blood pressure usually started to fall and often reached the usual stable fasting level but as soon as it did, compensatory mechanisms became overactive and caused the pressure to rise to high values and remain far above the usual fasting level. Pulse rates were the same or lower than during normal fasts.

The number of fat episodes necessary to produce the abnormality in the response to fasting varied from one to six. It also varied in the same dog. In Dog I in 1950, the abnormality developed after the second fat episode, while in 1952-54 it required 6 fat episodes to produce definite abnormality.

TABLE I

Dog	Values After Fasting			Values After High Fat Diet			Difference			Significance		
	S	D	P	S	D	P	S	D	P	S	D	P
I	(1)133	(1)54	(1)106	160	70	101	+27	+16	-5	<.01	<.01	<.02
II	119	49	72	162	64	89	+43	+15	+17	<.01	<.01	<.01
III	115	63	97	119	60	87	+4	-3	-10	>.05	>.05	<.01
				118	66	84	+3	+3	-13	>.10	>.05	<.01
IV	107	64	89	148	66	101	+41	+2	+12	<.01	>.10	<.01

A comparison of fasting, diets high in carbohydrate and diets high in animal fat as sensitizors of the blood pressure elevating effect of a balanced high calory diet.

Dog I (1) High calory diet following a diet high in carbohydrate.

III. *A Comparison of Fasting, High Carbohydrate or High Fat Diets as Sensitizors of the Blood Pressure Elevating Effects of a High Calory Diet.*

The remarkable effects of several previous fat episodes on the blood pressure during the metabolic stress of fasting raised the question as to the effect on blood pressure during the metabolic stress of a balanced high calory diet.

The high calory diet used contained one-half of the calories as horse meat and one-half as cracker meal and was fed at the luxus consumption level of 120 cal/M²/hr/24 hrs. This same diet had been studied on these 4 dogs in 1950-52 at which time they were sensitized by a prolonged preliminary fast (1).

Immediately after the sixth fat episode when they were known to be very sensitive to the metabolic stress of fasting, they were given this diet without a preliminary fast. The results on Dogs II, III and IV are shown in Table I. It is seen that in both Dogs II and IV the systolic, and in Dog II the diastolic pressures were significantly higher after sensitization with six fat episodes than they were after sensitizing by fasting. In Dog III the first experiment after the fat episodes was not significantly higher than after fasting. Later this was repeated with the same result.

In the studies on protein and carbohydrate (1), it was found that diets high in carbohydrate when fed after a prolonged fast caused a marked elevation of systolic pressure and pulse rate but this effect disappeared when the high carbohydrate diet was terminated and there were no abnormal after effects. The balanced high calory diet was fed to Dog I immediately after a high carbohydrate diet and later after six fat episodes, in both instances without an intervening fast. As seen in Table I, the blood pressure on this diet was much higher after the fat episodes than after a high carbohydrate diet.

These experiments show that in 3 out of 4 dogs a balanced high calory diet raised the blood pressure more when fed after several fat episodes than after fasting or a high carbohydrate diet, thus showing that the fat episodes sensitized the animals to the metabolic stress of a high calory diet as well as to that of fasting.

IV *Do Fat Episodes Sensitize to Other Stresses or Only to the Metabolic Stresses of Fasting and High Calory Diets?*

In order to answer this question the effect of work in a cage treadmill and exposure to cold (6-8°F) was studied in 3 dogs immediately after the fat episodes but no evidence was found indicating unusual sensitivity of the blood pressure elevating mechanisms to these stresses.

V *The Phenomenon of Momentum of the Metabolic Mill as it Influences Blood Pressure.*

Previous studies (8,9) suggested that the metabolic mill may show momentum if it is running at high speed because of a high calory diet. Under these circumstances considerable change may be made in the quality or quantity of the ingested fuel but the effect of these changes may not be immediately evident because of momentum. If this phenomenon is reflected in the metabolic effect on blood pressure, then a change in diet which should alter blood pressure may not show the anticipated or true change. Fasting until the pressure reaches the stable fasting value is a simple and effective means of decreasing momentum and for this reason a preliminary fast preceded each experimental diet in previous studies (1). In the present studies, very definite evidence of the effect of momentum on blood pressure was obtained. After the animals had been sensitized by six fat episodes they were placed on the balanced high calory diet and while the blood pressure was at the high values shown in Table I, the diet was changed to the usual kennel ration without an intervening fast. The results are shown in Fig. V. The control base lines represent the mean systolic and diastolic pressure and pulse rate as repeatedly determined on the kennel diet. It is seen that if the kennel diet was given when the momentum of the metabolic mill was high the blood pressure was initially very high in both dogs, but gradually diminished and reached the expected value in the 59-88 day period in Dog I and in the 38-57 day period in Dog IV. These studies clearly demonstrate the influence of momentum and unless it is taken into consideration in studies on the effect of diet on blood pressure, erroneous results will be obtained.

VI *Hematologic Studies.*

Before starting these studies the animals were standardized for 2 months during which eosinophile and total white cell counts were made daily and red cell counts and stained smears at frequent intervals. The same routine was continued during the two year study of high fat diets. Only a few of the salient features of these studies will be mentioned.

The eosinophile counts diminished during fasting. The high fat diets after fasting caused the counts to

TABLE II

Dog		Fasts	Fat Episodes		Kennel Diet After 1st 2nd and 4th Fat Episodes	
		Percent		Percent		Percent
I	1	–42[1]	1	–55	1	–25
	2	–65	2	–82	2	–32
200[3]	3	–82	3	–88	–	—
	4	–82	4	–75	4	–49
‡84	5	–70	5	–73	–	—
	6	–75	6	–82	–	—
	7	–85	–	—	–	—
						–54[2]
II	1	–38[1]	1	–60	1	–37
	2	–32	2	–85	2	–55
413[3]	3	–83	3	–78	–	—
	4	–82	4	–75	4	–70
‡175	5	–98	5	–79	–	—
	6	–70	6	–92	–	—
	7	–85	–	—	–	—
						–80[2]
III	1	–48[1]	1	–58	1	–58
	2	–68	2	–83	2	–70
291[3]	3	–79	3	–79	–	—
	4	–80	4	–92	4	–75
‡141	5	–90	5	–85	–	—
	6	–80	6	–92	–	—
	7	–88	–	—	–	—
	8	–85	–	—	–	—
						–75[2]
IV	1	–28[1]	1	–68	1	–42
	2	–63	2	–68	2	+12
448[3]	3	–48	3	–28	–	—
	4	–78	4	–75	4	–50
‡235	5	–65	5	–72	–	—
	6	–55	6	–82	–	—
	7	–78	–	—	–	—
						–80[2]

The eosinopenia during various phases of the experiments with diets high in animal fat expressed as percent difference from the control value.

(1) No fat diet before this fast.

(2) On kennel diet for 90 days after completion of all phases of the problem.

(3) Control values and standard deviation. Done after the experiments with carbohydrate and protein and just before first fat episode.

remain low and the percent decrease below the control values became greater with repeated fasts and high fat diets (Table II). This effect showed a carry over so that the eosinopenia was present not only on the high fat but also on the kennel and high calory balanced diets. Even today these dogs still have an eosinophilia of *70* to *80* percent below the original control level when on the usual kennel diet.

The total white cell count always diminished during fasting and rose often to very high levels (40,000-50,000), on the high fat diets.

The red cell counts remained above 5 million per cmm. in spite of the repeated fasting and realimentation with deficient diets. Nucleated red cells and high reticulocyte counts were found on 2 dogs during the high fat diet period. These findings suggest that some hematopoietic stimulus may have been operating during the period of the high fat diets.

VII *Obesity.*

After the 6 fat episodes the animals were placed on the high calory balanced diet and the blood pressure remained high as shown in Table I. They remained on the diet for *90* days and all became very obese. The obesity was confined to the back and neck, the legs remained surprisingly free of fat. The resemblance to the obesity in Cushing's syndrome was inescapable. Experiments still in progress show that the fat is retained with remarkable tenacity even when the animals are placed on very low calory diets.

DISCUSSION

When diets high in animal fat were repeatedly fed following prolonged fasts they gradually brought about changes in the homeostatic mechanisms regulating blood pressure which had the following characteristics:—(1) The pressure was normal when the animal was receiving an optimal non-stress diet. (2) The pressure became abnormal when the animal was subjected to the metabolic stresses of fasting or high calory diets.

When an animal previously sensitized by fat was fasted the systolic and diastolic pressures usually showed an initial fall to approximately the usual stable fasting values but this was followed by a rapid rise of both to high values and they did not reach the usual stable fasting values even though the fast lasted several weeks. The pulse rate was usually not significantly different from that during a normal fast.

Fasting has been identified as a typical alarm reaction (10). In the early stages of fasting, the behavior of the blood pressure of a normal dog shows alternate tendencies to fall (shock phase of the alarm reaction) and rise (counter shock phase). As the fast continues the counter shock phase gradually becomes weaker and finally the shock phase predominates and the pressure falls to the stable fasting value. Previous studies (6) have shown that luxus consumption diets preceding a fast, intensify the counter shock phase so that the time required to reach the stable fasting level is prolonged but the general trend of the pressure is definitely downward. After sensitization with fat, however, the counter shock phase becomes so dominant that the blood pressure may rise rather than fall during fasting. This abnormality may be dormant for 50 days or more[3] while the animal is on an optimal non-stress diet.

The second abnormality produced by repeated fat episodes was the intensification of the blood pressure elevating effect of the balanced high calory diet. In this respect, high fat diets sensitized more than a previous fast while a previous luxus consumption diet high in carbohydrate caused little or no sensitization.

Previous treatment with fat did not appear to sensitize the blood pressure elevating mechanisms to the other stresses studied (cold and work on a treadmill).

The progressively increasing eosinopenia after repeated fat episodes was very striking and roughly paralleled the development of the abnormal blood pressure responses to fasting. The eosinopenia during the first fasts, which were not preceded by fat episodes, was always less than 50 percent below the control value in these four dogs but it increased progressively as the fasts were preceded by an increasing number of fat episodes. It is generally agreed that factors other than the adrenal cortical hormones may cause eosinopenia, but since the eosinopenia and increased capillary resistance seen in fasting are both abolished by STH (11), it appears that adrenal cortical hormones play an important role in the eosinopenia of fasting.

Unfortunately, the capillary resistance could not be studied on the four dogs used here because the repeated dietary stresses to which they were subjected during the studies on protein and carbohydrate had resulted in a fixation of the capillary resistance so that it did not rise during fasting or dietary stress. (This phenomenon has been observed and reported previously (12)). The possible role of STH and other pituitary-adrenal hormones in the fixation of capillary resistance by dietary stresses can only be conjectured.

Because of the pronounced eosinopenia, the abnormally high blood pressure during metabolic stresses, and the distribution of the fat in obesity, it is tentatively suggested that the stress of repeated fasting and realimenation with high fat diets caused abnormalities in the secretions of the pituitary-adrenal cortical system.

These animals appear to be potentially hypertensive and it is possible that if they were subjected to factors which would cause constant stimulation of their blood pressure elevating capacities, actual hypertension might develop.

Other investigators have shown that diets high in fat cause several deleterious changes in the cardiovascular system which are not shared by carbohydrate or protein. Holman has shown (13,14,15,16,17) that diets high in fat when combined with a minimal kidney lesion, produce widespread necrotizing arteritis. It is possible that the repeated administration of high fat diets following prolonged fasting may produce minimal changes in the arterioles so that they become abnormally sensitive to the vasoconstrictor effects of certain neurohormonal factors which may become active in response to fasting or high calory diets.

Diets high in fat also have been reported to increase the viscosity of the blood (18), hasten coagulation (19) and cause adhesiveness and a tendency for the red blood cells to clump so that miliary emboli may result (20,21).

High fat diets also cause marked enlargement of the adrenal glands in rats (10). A carry-over of the effect of a previous high fat diet is suggested by the studies of Deul and Hallman (22). It may be significant in relation to the present study that the blood pressure is strikingly low in both idiopathic and symptomatic steatorrhea (23).

SUMMARY

1. Dogs were subjected to repeated prolonged fasts and realimentation with diets containing 50 percent or more of the calories from beef suet or butter (fat episodes). This was repeated six times during a period of two years. As a result of this procedure, the following changes gradually developed in each of four dogs.

(a) A change in the response of the blood pressure to fasting, so that the fall characteristic in normal dogs was replaced either by a failure to fall or by a progressive rise to high levels. Heart rate was not significantly different from that in fasts in which the blood pressure showed the usual fall. If the animals were receiving an optimal non-stress diet after the fat episodes the blood pressure would remain at the control level for 50 days or more but the abnormality was dormant and would appear as soon as the stress of fasting started. The blood pressure while on the high fat diet was not predictable, usually it was normal or low, less often higher than normal.

(b) After several fat episodes, the blood pressure was abnormally high on a balanced high calory diet. Several fat episodes sensitized the blood pressure response to high calory diets more than a preliminary fast.

(c) Parallelling the above changes, the animals developed a very pronounced and persistent eosinopenia.

(d) Three of the dogs sensitized by several fat episodes were subjected to the stress of muscular work (treadmill) or to cold but the blood pressure responses were not exaggerated.

It is suggested that sensitization by several fat episodes may render an animal potentially hypertensive as disclosed in the abnormality of the responses to the metabolic stresses of fasting and high calory diets.

1. Aided by Grant H-1014, National Heart Institute, National Institutes of Health.

2. Multicebrin tablets (Lilly) contain the daily human requirements of the common vitamins.

3. Studies still in progress on these dogs show that the period of dormancy may last as long as six months.

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TRANSPARIETAL SPLENIC VENOGRAPHY AND SPLENIC ARTERIOGRAPHY—THEIR USE FOR VISUALIZATION OF LIVER AND SPLEEN AND THEIR IMPLICATION FOR THE DIAGNOSIS OF PANCREATIC LESIONS

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RADIOGRAPHIC demonstration of the venous and arterial systems of the viscera within the upper abdomen represents an advance in our diagnostic procedures. The possibilities of venography and arteriography as aids in the differential diagnosis of upper abdominal lesions are as yet not fully explored. The purpose of this paper is to discuss some of the diagnostic potentialities of these procedures based on our own experience.

INTRINSIC LIVER DISEASE AND ROENTGEN DIAGNOSIS

Intrinsic diseases of the liver could not be diagnosed radiographically on plain films of the abdomen. Only in the presence of abnormal calcifications, air, or abnormal amounts of fat has the roentgen examination yielded information other than the shape of the intra-abdominal organs. The introduction of the pneumoperitoneum offered a better method for radiologic demonstration of the outline of intra-abdominal organs and for their differentiation from surrounding structures. This method, however, does not disclose any structural alterations within these organs. Oral and intravenous cholangiography added useful diagnostic information inasmuch as they outlined the extrahepatic biliary duct system and occasionally disclosed some abnormal communication between the ducts (as in abscesses), or showed displacement of the ducts by tumor. The latter, however, was a rare finding. The use of thorotrast

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Submitted Feb. 3, 1955.

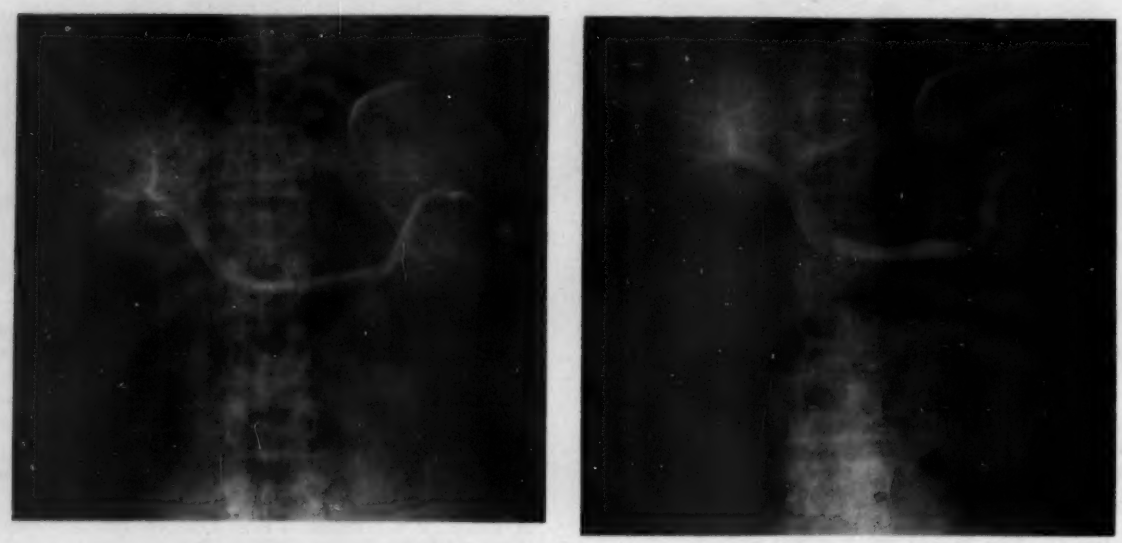

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Fig. 1. Normal transparietal splenic venogram. The normal caliber of the splenic and portal veins is shown. In B, in addition to the demonstration of the smaller branches of the portal circulation, opacification of the entire liver is noted. The spleen is unusually well outlined because of the collection of dye within the splenic capsule.

which was introduced by Radt (1) and Oka (2) for visualization of the structures of the liver and spleen has been generally abandoned because of the permanent deposition of this contrast medium in the reticulo-endothelial system and the resulting permanent radio-activity.

HISTORY AND TECHNIQUE OF TRANSPARIETAL SPLENIC VENOGRAPHY

Abbeatici and Campi (3,4) in 1951 after experimental work in animals introduced transparietal splenic venography. It consists of the injection of a radiopaque dye into the splenic pulp after puncture of the spleen. Urokon Sodium 50% was exclusively used in our series. From the splenic sinuses the dye enters the splenic vein and the portal circulation. If enough dye has been injected and films are secured at three second intervals for a period of twelve to fifteen seconds, the portal system within the liver will be filled with dye and a radiographic outline of the intrahepatic portal circulation can be obtained. The procedure is extremely useful in disclosing radiographically the internal structure of the liver. It is less complicated than the procedure of puncture of the portal vein through the abdomen as proposed by Steinbach and co-workers (5).

In this country most reports dealing with transparietal splenic venography state that the procedure was carried out in the Operating Room under general anaesthesia. In our institution we perform the procedure under local and Trilene anaesthesia in the Roentgenological Department, employing a fractionated technique and manual change of films. Transparietal splenic venography represents a distinct advantage in that we have a relatively innocuous method of demonstrating the vascular bed of the liver. The disadvantage of this procedure lies in the fact that we have to employ anaesthesia because of the pain associated with the injection of the dye. Selection of patients for this procedure has to be made with three main rules in mind: 1) Renal function must show no impairment; 2) Absence of dye sensitivity; 3) Bleeding time should be normal.

Splenic puncture is quite widely used nowadays by hematologists, and if used with proper care is not dangerous. The procedure is easily carried out if the spleen is enlarged or palpable. In small spleens the procedure is not readily accomplished. Inadvertent entry into the stomach has been reported by the Mayo Clinic with no untoward effects (6). We have inadvertently entered the colon in one case without any untoward results. In considering the procedure one should weigh the possible diagnostic information to be gained, against the possible risk.

SCOPE OF TRANSPARIETAL SPLENIC VENOGRAPHY

Transparietal splenic venography has been mainly used in the diagnosis of portal hypertension, intra- and extra-hepatic, and as a pre-operative guide to the surgeons to establish the feasibility of a porto-caval anastomosis or of a spleno-renal shunt (7). It is obvious that in the presence of thrombosis of the portal vein a different abdominal incision is needed to perform a spleno-renal shunt. Transparietal splenic venography can show the portal circulation in its normal and abnormal states, and it is helpful in the diagnosis of cirrhosis of the liver (Fig. 1). It also can demonstrate space occupying lesions of the liver which will compress the intra-hepatic circulation, such as primary or secondary neoplasms, ecchinoccous cysts, multiple cysts, hemangioma, syphiloma, adenoma, liver abscesses, etc.

We have performed the procedure in 14 different instances, most of them presented problems of intra-hepatic pathology as tumor metastases, intra-hepatic cysts or hemangioma and cirrhosis of the liver.

METASTATIC DISEASE OF THE LIVER

Isolated or widespread metastases which are situated

in the liver substance will give rise to translucent zones in the hepatograms due to compression of the sinusoids by the metastatic nodules (Fig. 2, 3, 4, 5). If the metastases are situated near the hilus, they produce compression of the portal vein and an insufficient amount of dye enters the liver parenchyma to produce a hepatogram. Narrowing of the main portal vein and its branches is the main phenomenon observed roentgenographically. Rigler (8) who obtained visualization of the liver parenchyma after translumbar aortography made similar observations in regard to the presence of negative zones within the liver in the presence of metastases. Our interest in obtaining diagnostic data in the presence of metastases of the liver was stimulated by the desire of applying the methods of venography and arteriography for the introduction of chemotherapeutic agents. Such procedure might open a more direct approach to these lesions. It is, however, already obvious from our diagnostic studies that chemical substances reach the healthy liver in greater concentration than they could reach the malignant deposits within the liver. Rigler (8) quotes Lewis that metastases in the liver are deficient in circulation. This seems to confirm our own impression. Transparietal splenic venography is not ideal for complete visualization of the spleen proper. Only a portion of the spleen is usually opacified since the dye immediately after injection leaves the spleen entering the splenic vein.

HEMANGIOMA OF THE LIVER

We have had one instance of hemangioma of the liver proven at operation in which splenic venography yielded considerable information. Because of the unusual interest, this case will be reported in detail here.

Case History: A 64 year old white female was admitted to the Jewish Chronic Disease Hospital on March 15, 1953, with the diagnosis of carcinoma of the breast with metastases. She had a lump in the right upper quadrant of the right breast measuring 5 x 3 cm, which appeared to be freely movable. Aspiration biopsy revealed a ductal cell carcinoma. There were no palpable lymph nodes, but there was another palpable mass in the right epigastric region which was movable with inspiration and seemed to be within the liver.

Past history revealed diabetes and hypertension of ten years duration; several cerebral vascular accidents had subsided without any loss of function. Because of the presumptive diagnosis of a metastatic breast carcinoma, the patient was admitted to our institution for radiation therapy. Information obtained from her family physician suggested that the abdominal mass had not been noted previously. The breast tumor received intensive radiation therapy and disappeared completely. In the absence of a histological diagnosis of the epigastric mass, this was not treated with radiation. Since the patient did extremely well for almost one year without evidence of new metastases and without any change in the size of the palpable epigastric mass, a liver biopsy was attempted. Because of massive bleeding, no definitive diagnosis could be established. The material obtained by punch biopsy did not show any tumor cells. To evaluate further the character of this mass, transparietal splenic venography was carried out.

The essential features in the roentgenograms obtained consisted of a marked compression of the splenic

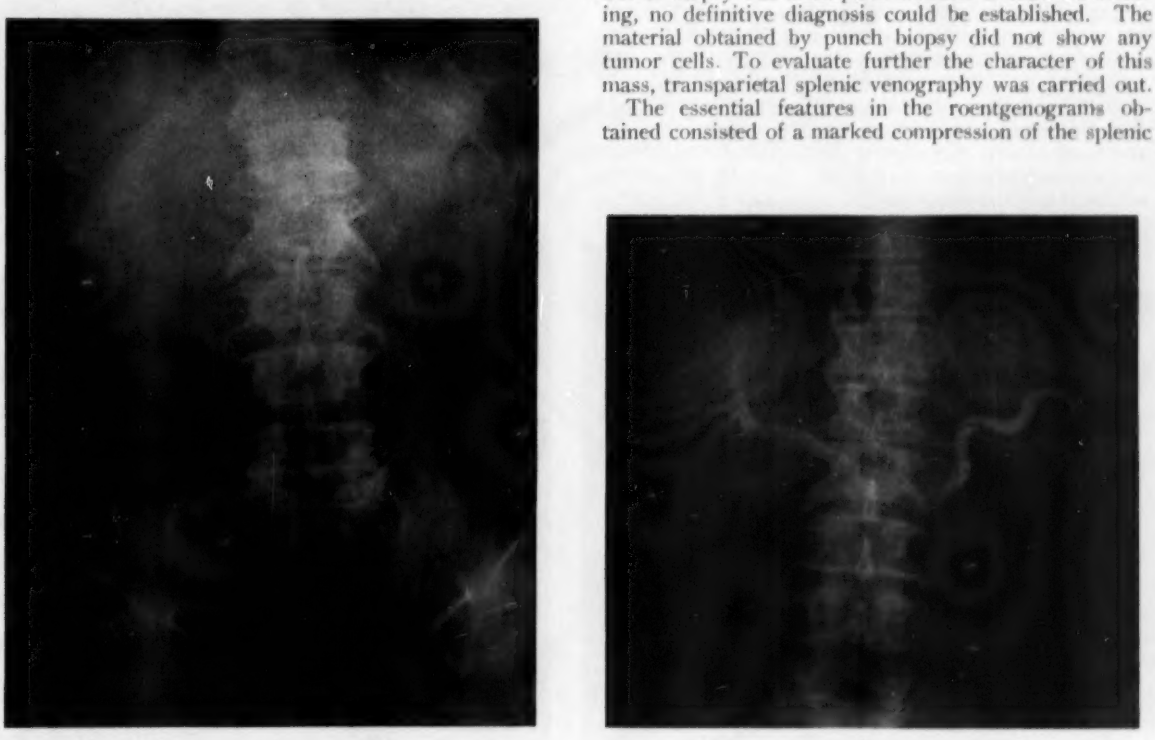

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Fig. 2 Flat plate of the abdomen (A) and injection of 10cc of Urokon Sodium (50%) into the splenic pulp by the transparietal route (B). The lumen of the splenic and portal veins appears to be normal, and the right and left main branches are also well filled. This patient, age 72, male, had an exploratory laparotomy one year previously with the diagnosis of metastatic medullary anaplastic carcinoma from an omental node. The lesion probably orginated in the transverse colon. Metastases were present within the liver at the time of exploration. The liver appeared to be enlarged and hard to palpation.

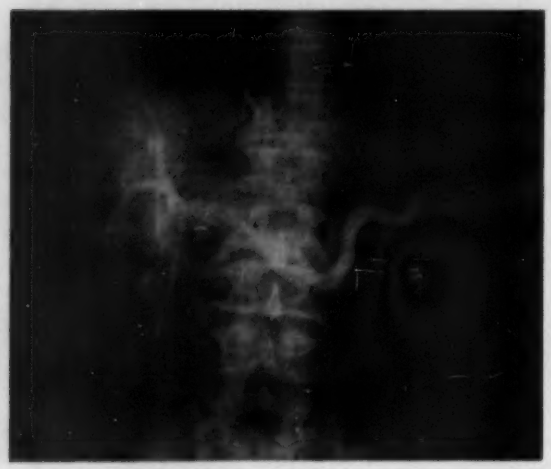

Fig. 3. After completion of the injection of a total of 35 cc of Urokon Sodium the entire portal circulation is outlined and a beginning hepatogram is noted. Same patient. The liver edge is seen above the iliac crest. The distal branches are narrowed.

vein by a large intrahepatic mass (Fig. 5,6). This compression was most marked at the junction of the splenic and portal veins, and interfered with the free flow of dye into the portal vein. There was also marked filling of the collateral circulation. The inferior mesenteric vein was filled, as well as a network of veins around the spleen communicating with gastric and pancreatic veins. Such marked collateral circulation is similar to that observed in portal hypertension. The differentiating main feature was the compression and displacement of the splenic vein. We noted also a marked displacement of the left main branch of the portal vein. This branch curved in a convex fashion towards the right side.

On April 13, 1954, the patient was taken to the operating room and a huge mass occupying the left lobe of the liver was found. The mass was multi-nodular, cystic to palpation, and dark brownish blue. The remainder of the exploration was negative. The left triangular ligament was cut and the esophageal junction of the stomach was pushed to the side. By using multiple clamps and mattress sutures, the left lobe of the liver just proximal to the origin of the tumor mass was incised through and the specimen removed. There was no excessive bleeding during the procedure.

Sectioning of the main mass disclosed an intricate intercommunicating pattern of vascular channels of variable diameters, and the diagnosis of venous angioma of the liver was made. There was no evidence of tumor metastases.

Usually hemangioma of the liver is an incidental finding at post mortem examinations. Occasionally the hemangioma is large enough to give rise to clinical symptoms and manifests itself as an abdominal mass. Rarely a hemangioma of the liver may rupture and cause intra-peritoneal bleeding. Most hemangiomata are small in size and multiple. They can be associated with other abnormalities such as hemangioma of the skin, cystic kidneys, etc. Schumacher (9) collected 66 cases of hemangiomata of the liver which had been operated upon. There is no predominance of either sex and no particular age group involved. The etiology of hemangiomata is unknown. A constitutional defect is most commonly considered. In addition to the clinical signs, the roentgen examination may at times suggest the presence of a hemangioma because of the evidence of calcification in the hepatic area on a plain film of the abdomen. Calcification, however, is only present in a relatively small number of cases. If a hemangioma is

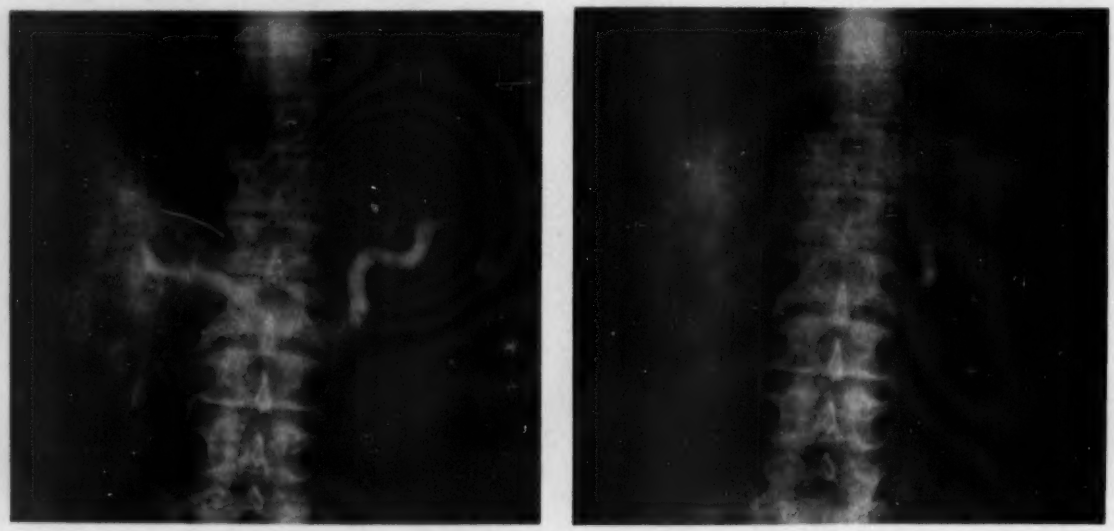

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Fig. 4. (A) Same patient, three seconds and nine seconds (B) later after completion of injection. Numerous translucent zones representing metastases are now demonstrated within the liver. (B) The dye has disappeared from the portal vein. The metatases are more clearly defined. A small residue of dye is noted within the spleen at the puncture site and in the splenic vein. A film ten seconds later no longer disclosed any opacification.

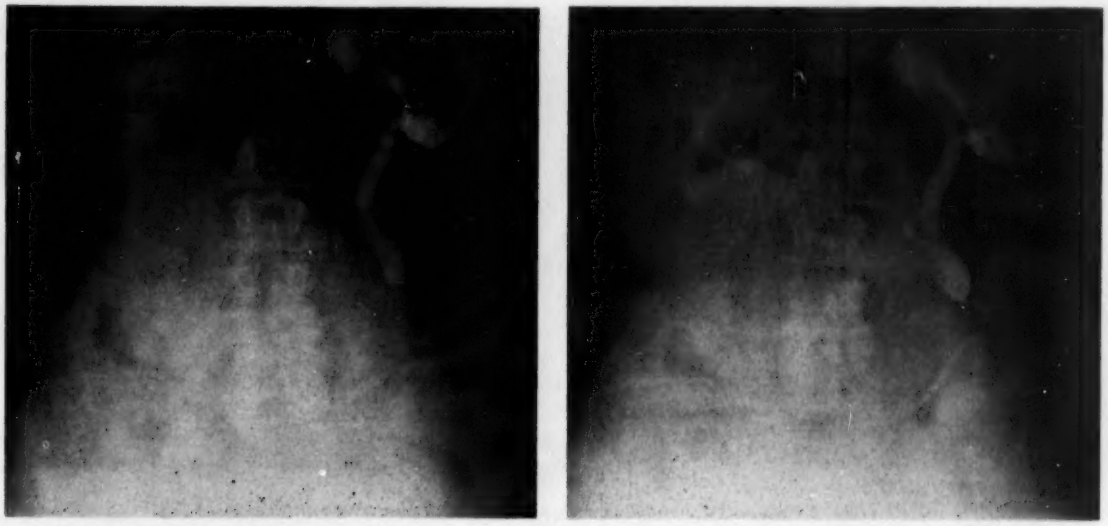

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Fig. 5. Transparietal splenic venography in hemangioma of the liver. Marked filling of the collateral circulation around the spleen and filling of the inferior mesenteric vein is noted. Compression of the distal portion of the splenic vein is present. A large circular negative zone representing the hemangioma is present within the left lobe of the liver. The hemangioma did not opacify.

large enough, displacement of neighboring structures can be demonstrated radiographically. With the use of transparietal splenic venography a diagnosis of an intrahepatic mass can be established. Where there is free communication between the hepatic artery and the hemangioma, hepatic arteriography may be even of greater help and permit a clear and direct demonstration of the vascular mass. Felsen (10) has reported such an instance.

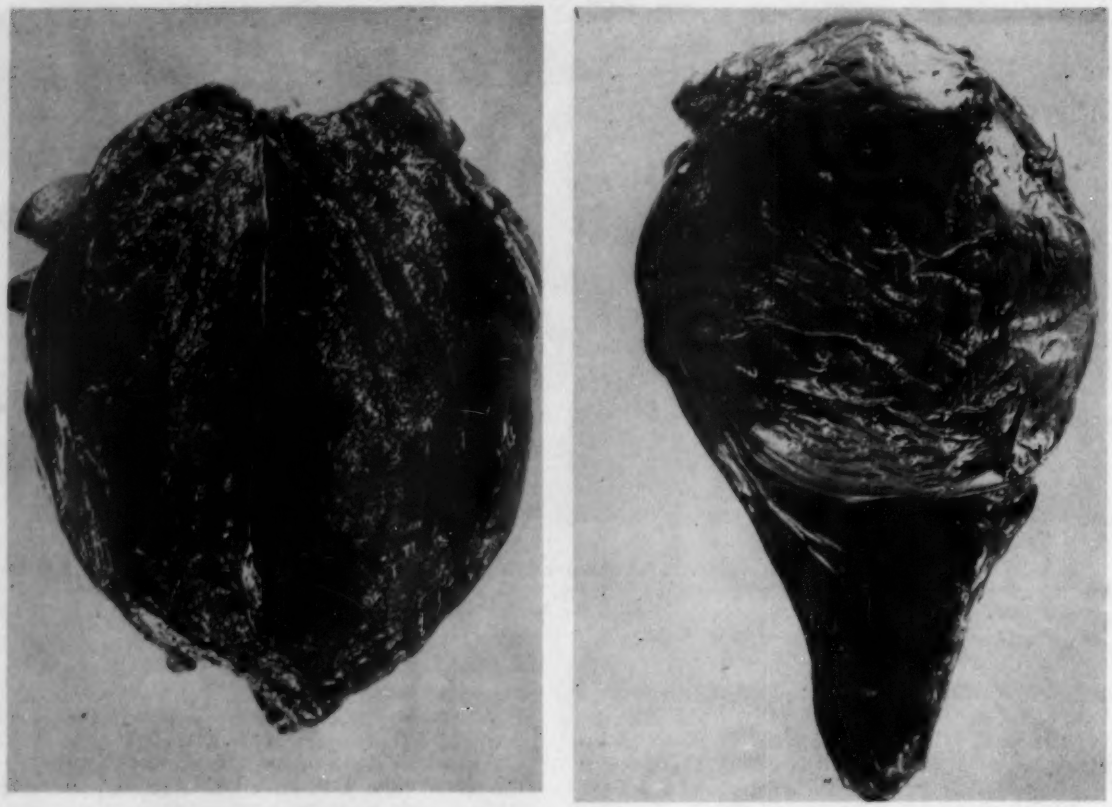
SPLENIC ARTERIOGRAPHY

Rigler and Olfalt (8) used 40 cc Urokon Sodium (70%), injecting it through a size 16 needle rapidly into the thoracic aorta at the level of D 11. By this method the celiac axis, the splenic and hepatic arteries are well filled with dye. The entrance of the contrast medium into the liver is accomplished in two ways: 1. by the direct entry of the dye from the abdominal aorta into the hepatic artery and the liver parenchyma, and 2. by the return flow of dye from the spleen, and the return flow of the superior mesenteric vein which form the portal circulation. Through this method we have demonstrated intrinsic diseases of the liver in several instances.

We have modified Rigler's method of injection to a direct injection into the aorta at the level of the splenic artery, so-called splenic arteriography (11) (Fig. 7). Since transparietal splenic venography gives us the desired information about the internal structure of the liver, we see no need for a hepatogram through translumbar aortography. Splenic arteriography offers, however, valuable additional information through the visualization of the splenic artery and the spleen itself. The procedure consists of the direct injection of 20-30 cc of Urokon Sodium (70%) at the level of the splenic artery into the aorta. The aorta is punctured and a test film is obtained to check the position of the needle. The aortic puncture is carried out by placing the needle below the rib margin on the left side at four fingers breadth from the midline. A 17" gauge 7" long needle is used to which polyethylene tubing is attached. The direction of the needle is toward the acromial process of the right side. After the aorta is penetrated at the described level, the bevel of the needle is directed toward the left side. A test injection of 5 cc of Urokon Sodium is made which checks the position of the needle in relation to the splenic artery. This film is developed, and if the puncture site has been selected accurately, it will show dye within the splenic artery. A second film is then exposed and immediately developed to check whether the dye is properly cleared through the kidney. Then 20-30 cc of Urokon Sodium is injected through the automatic injection apparatus described by Langsam (12) and films are obtained with the aid of the Fairchild magazine at two second intervals for a period of eighteen seconds. These will demonstrate the outlines of the splenic artery, of the spleen itself and of the splenic as well as the portal veins.

POSSIBLE USE IN DIFFERENTIAL DIAGNOSIS OF PANCREATIC PATHOLOGY

In addition to demonstration of the vascular bed of the spleen, the procedure may uncover indirectly any lesion within the tail or the body of the pancreas. Such lesions are likely to displace the splenic vessels or to cause thromboses in these vessels. The body and tail of the pancreas lie obliquely over the upper pole of the left kidney and within the triangle formed by the splenic artery and the splenic vein. The lower pole of the spleen forms the apex of this triangle. Lesions of the body or the tail of the pancreas are usually silent until they reach a considerable size. The paucity of confirmatory or diagnostic roentgen evidence, aside from the changes which can occasionally be encountered in the intravenous pyelogram or films of the upper gastrointestinal tract, stimulated our interest in this subject.



A

B

Fig. 6. The operative specimen open and closed is portrayed. Histological diagnosis—Venous Hemangioma of the liver.

Compression of the blood vessels in the left renal area by large lesions of the body or tail of the pancreas may occasionally result in loss of function of the left kidney. Thus Chamberlin (13) as well as Poppel (14) have described that abnormalities in the left pyelogram enabled them in conjunction with suggestive clinical findings to make the presumptive diagnosis of pancreatic tumors. Likewise, such tumors may displace or compress the splenic artery or vein. Splenic arteriography will easily demonstrate such vascular derangement. The addition of this method to our differential diagnostic procedures may be particularly important since lesions in the tail or body of the pancreas are more readily accessible to surgical treatment than those in the pancreatic head. Cancer of the pancreas is a not uncommon tumor, it occurs more frequently in males than in females of the older age group. Loss of appetite, loss of weight, ill defined pain radiating to the back and left shoulder, are suggestive of involvement of the pancreas, when more common disorders are excluded. Persistent diarrhea is occasionally found. Thrombophlebitis of the lower extremities may indicate the presence of a lesion in this region. In ill defined syndromes of this kind, splenic arteriography may be indicated as a differential diagnostic procedure.

POSSIBLE RISKS OF THE PROCEDURES

As we add new diagnostic procedures the risks involved have to be weighed against the possible diagnostic information to be obtained. Our experience is still limited. We have carried out the splenic arteriography only five times, each time without untoward sequelae. In one case it confirmed the tentative diagnosis of a splenic artery aneurysm made on the plain film (Fig 8). This case has been recorded by Langsam, Lewitan and Wilensky (11). In another one it added to the other clinical data to help exclude a lesion within the tail of the pancreas. We are convinced that this new approach merits further clinical investigations.

Accidental injection of one of the major visceral arteries has been reported by Smith and his associates (15) in 1952. They cite ten such instances without any major complications. They reported a total of 800 arteriograms without a fatality. Death and gangrene of the bowel were reported by Vitte (16), following accidental injection of 80% Sodium Iodide into the superior mesenteric artery. All deaths or gangrenes reported were caused by the use of Sodium Iodide. In the course of over 100 translumbar aortographies with Urokon Sodium (70%) we have filled the visceral arteries with dye many times without harm. One should guard, however, against direct injection into the renal arteries under all circumstances. A test injection of 5 cc to check the position of the needle eliminates the dangerous possibility of overloading the renal circulation with large amounts of contrast medium. We feel that the injection of Urokon Sodium into the splenic artery carried out under proper care and with well considered

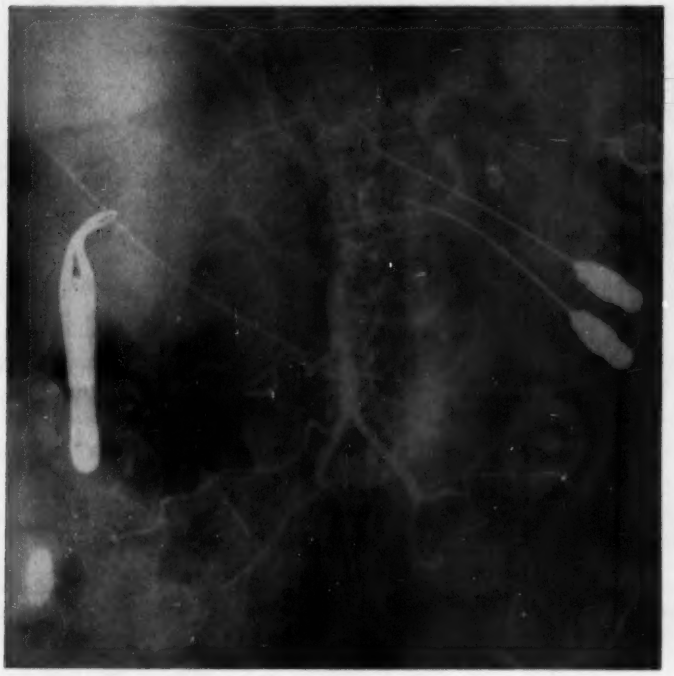


Fig. 8. Opacification of an aneurysm of the splenic artery, also visualization of the superior mesenteric artery and its branches.

indication will yield valuable information and is a relatively safe and harmless procedure.

SUMMARY AND CONCLUSIONS

Transparietal splenic venography, as introduced by Abbeatici and Campi permits the radiographic demonstration of the intrinsic structure of the liver. It is useful in the diagnosis of space occupying lesions within the liver. Detailed venographic studies are presented which demonstrate the presence of liver metastases and a hemangioma in the liver. A modification of translumbar aortography, so called splenic arteriography, is described. The application of radiologic visualization of the spleen and its artery and vein for the differential diagnosis of space occupying lesions in the body or tail of the pancreas is suggested.

The authors are indebted to Dr. Louis Nathanson, Director of the Department of Radiology of The Jewish Chronic Disease Hospital for his valuable advice.

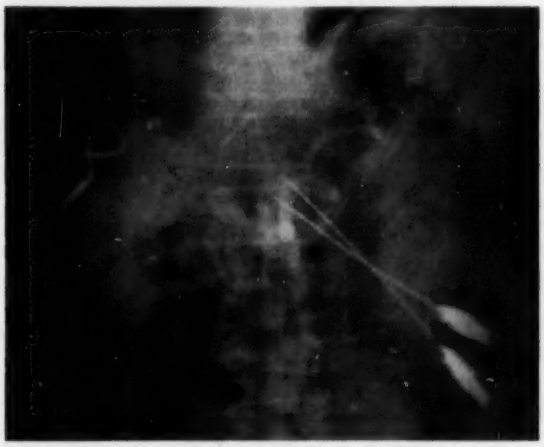


Fig. 7. Injection of the aorta at the level of the splenic artery. The splenic artery, the spleen and the splenic and portal veins are clearly demonstrated. Normal findings.

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PRECIPITIN TEST FOR SERUM LIPOPROTEINS IN HUMAN CORONARY ATHEROSCLEROSIS

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THE STUDIES of Kunkel (1), Gitlin (2), and Baker et al (3), have demonstrated the immunochemical heterogeneity of human plasma B-lipoprotein. Gofman et al (4), have found that serum lipoproteins are heterogeneous as demonstrated by Svedborg flotation rates in the ultracentrifuge in a sodium chloride solution of 1.06 density.

The studies of Baker et al (3), described a simple serological method for differentiating abnormally increased serum lipoprotein concentrations in experimental animals. By the immunization of rabbits with lipoprotein fractions, Baker produced immune sera which detected abnormally increased concentrations of dog serum lipoproteins in dogs on a thyrogenic diet. Recently, Grant and Berger (5), corroborated these findings and also demonstrated that a highly positive correlation existed between the quantity of precipitate obtained in the precipitin test and the total lipoproteins measured by the ultracentrifuge. They also found that it was possible to establish a precipitin titer for human serum with antisera prepared in chickens against human lipoproteins. In the present report, initial results are presented on the application of such precipitin tests clinically in man for the detection of atherosclerosis.

Abnormal serum lipoproteins were found to be correlated with the presence of human coronary atherosclerosis by Gofman et al (4), through ultracentrifugal analysis. It appeared to be of interest to explore the clinical application of this precipitin test to human sera, particularly those with atherosclerosis. Accordingly, the authors selected a series of proven cases with recent coronary thrombosis and myocardial infarction as the best criteria for the presence of human atherosclerosis of the coronary arteries as Morrison and others have pointed out (6).

EXPERIMENTAL

Sera were pooled from the blood of 4 men (35 to 57 years old) who had recent coronary thrombosis and myocardial infarction. The pooled serum was centrifuged in a preparative ultracentrifuge to separate the Sf 0-400 fraction high in lipoproteins.* Ten ml of serum were adjusted to a density of 1.062 plus/minus 0.001 by the addition of 22% sodium chloride solution. Twelve ml of this serum preparation were placed in a Spinco Model preparative ultracentrifuge for 10 hours at 40,000 rpm (105,000 x g) at a temperature of 15° plus/minus 1° C. The top 1.2 of this preparation was then withdrawn by means of a curved capillary tube attached to a 2 ml glass hypodermic syringe. This fraction represents a lipoprotein concentration 6 times that of the unfractionated serum. Of this supernatant fraction, 0.8 ml was placed in the analytical Spinco Model E ultracentrifuge at 59,780 rpm (260,000 x g) for 30 minutes at a temperature of 27° C plus/minus 1° C. Photographs were taken at intervals while the centrifuge was at speed. From these photographs, lipoprotein peaks and the lipoprotein concentration of the fraction were determined.

Baker and his coworkers (2) found that it was possible to prepare antisera in rabbits against lipoproteins. From their work, it appeared plausible that precipitin tests could reveal the presence and concentration of abnormal lipoproteins. This antigen was injected into rabbits and immune serum was prepared as described by Baker et al (2). For the tests reported here, three such sets of immune sera were required. The directions of Baker et al (2) were followed and modified for the precipitin tests. The tests were interpreted as follows: positive—definite flocculation with precipitate at the bottom of the tube; doubtful—a feathery flocculation; and negative—entirely clear. The tests were performed within one to four weeks after collection of the immune serum. The serum was kept at 4° C. After four weeks, the serum became useless for testing in that flocculation was obtained with all human sera at all test dilutions.

Human serum for testing was obtained from 36 males (38 to 79 years old, average 57 years) who showed proven evidence of coronary thrombosis and myocardial infarction (coronary atherosclerosis). For controls, 11 males (32 to 70 years old, average 57) and 6 females (29 to 54 years old, average 38 years) were selected who had no history of recent disease or clinical evidence of atherosclerosis. To supplement the control group, 12 males (32 to 59 years old, average 45 years) and

1. The Medical School, College of Medical Evangelists, and the Crenshaw Hospital.

2. Aided by a Research Grant from Baxter Laboratories, Morton Grove, Illinois.

Submitted, March, 1955

*Prepared by the Institute of Medical Physics, 1030 Sixth Avenue, Belmont, California.

TABLE I. PRECIPITIN TESTS WITH SERA FROM MYOCARDIAL INFARCT CASES AND CONTROLS AGAINST HUMAN LIPOPROTEIN ANTIGEN TREATED RABBIT SERUM.

Group	No. and Sex of Subjects	Response	Precipitin Test Dilution 1:200	1:400	1:800	1:1600	1:3200
Coronary cases	36 males	positive	34	23	13	2	1
		negative	1	5	17	25	29
		doubtful	1	8	6	9	5
	8 females	positive	8	5	3	0	0
		negative	0	0	2	7	7
		doubtful	0	3	3	1	1
	44 Sum of M and F	positive	42	28	16	2	1
		negative	1	5	19	32	37
		doubtful	1	11	9	10	6
Controls — normal	11 males	positive	11	1	0	0	0
		negative	0	10	0	0	0
		doubtful	0	0	0	0	0
	6 females	positive	6	3	1	0	0
		negative	0	2	4	6	6
		doubtful	0	1	1	0	0
	17 Sum of M and F	positive	17	4	1	0	0
		negative	0	12	15	17	17
		doubtful	0	1	1	0	0
Controls — miscellaneous diseases	12 males	positive	12	5	4	1	1
		negative	0	6	7	10	10
		doubtful	0	1	1	1	1
	12 females	positive	11	4	1	1	1
		negative	1	7	10	10	10
		doubtful	0	1	1	1	1
	24 Sum of M and F	positive	23	9	5	2	2
		negative	1	13	17	20	20
		doubtful	0	2	2	2	2
Controls — summary	23 males	positive	23	6	4	1	1
		negative	0	16	18	21	21
		doubtful	0	1	1	1	1
	18 females	negative	17	7	2	1	1
		positive	1	9	14	16	16
		doubtful	0	2	2	1	1
	41 Sum of M and F	positive	40	13	6	2	2
		negative	1	25	32	37	37
		doubtful	0	3	3	2	2

12 females (22 to 84 years old, average 55 years) were selected from patients having no clinical signs of heart involvement or atherosclerosis but having various diseases which did not involve the cardio-vascular system and had no known disorder or lipid metabolism (such as xanthomatosis, myxedema, nephrosis, etc.).

RESULTS

Pertinent data are summarized in Table I. Statistical analysis of part of these data is shown in Table II.

Significant differences in various situations were found at the 1:400 and 1:800 dilution levels. The difference in the series' response to the precipitin test between the coronary cases and the controls at the 1:400 level of dilution was highly significant. A significant difference was apparent at the 1:800 dilution level for these groups. The possibility of a greater separation of the series of coronary cases from the controls appeared when the coronary cases at the 1:400 level were compared with the controls at the 1:800 level. This was further emphasized in that the coronary cases gave a significantly different response at the 1:400 level as compared to the 1:800 level while the controls were not significantly different at these levels.

There were no significant sex differences in the coronary cases or in the control series. In so far as the precipitin tests were concerned, the choice of the control subjects did not appear to be influenced by the various diseases listed above.

DISCUSSION

The results reported here and by Baker et al (2), and Grant and Berger (3), demonstrate the practicability of developing a simple serological test for human serum lipoproteins. At present, these tests are complicated by the use of more or less mixed lipoprotein fractions. Although the source of the human sera was from cases expected to be high in abnormal lipoproteins, contamination from other serum proteins—particularly albumin—was likely. Nevertheless, a group of atherosclerotic cases could be statistically separated from a group of control subjects by the precipitin test using immune sera prepared from this complex source.

SUMMARY

Significant differences in response to the precipitin test as based on human serum lipoproteins were demonstrated between atherosclerotic cases and controls. These differences were not influenced by the sex of the subjects.

TABLE II. CHI-SQUARE ANALYSIS OF VARIOUS SERIES IN TABLE I.

Situation	χ^2	Probability of a Difference (P value *)	Significance of a Difference between Series
Sum of all of the coronary cases 1:400 vs. Sum of all of the controls 1:400	27.0	0.001	significant
Sum of all of the coronary case 1:800 vs. Sum of all of the controls 1:800	10.8	0.02	significant
Sum of all of the coronary cases 1:400 vs. Sum of all of the controls 1:800	38.4	0.001	significant
Sum of all of the coronary cases 1:400 vs. Sum of all of the coronary cases 1:800	11.7	0.01	significant
Sum of all of the coronary cases 1:800 vs. Sum of all of the controls 1:400	4.0	0.3	not significant
Sum of all of the controls 1:400 vs. Sum of all controls 1:800	3.5	0.3	not significant
36 male coronary cases 1:400 vs. 8 female coronary cases 1:400	6.6	0.1	not significant
36 male coronary cases 1:800 vs 8 female coronary cases 1:800	2.1	0.5	not significant
23 male controls 1:400 vs. 8 female controls 1:400	1.8	0.5	not significant
23 male controls 1:800 vs. 18 female controls 1:800	0.9	0.8	not significant

* Degrees of freedom = 3.

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ETIOLOGY OF THE DIABETIC NEUROPATHIES

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DESPITE THE enormous advances in knowledge of the fundamental problems involved in diabetes itself, the mechanisms responsible for the production of diabetic neuropathy have not been clarified, and its etiology is still a subject of considerable disagreement. This confusion is due, in great part, to disorders which so often and so characteristically complicate diabetes. The most common and most important of these complications is peripheral atherosclerosis which may, of its own accord, initiate neuritic symptoms. Complications such as this have made the evaluation of the etiologic factors in diabetic neuropathy difficult.

While the defect may possibly lie in disturbed fat metabolism, the nature of the biochemical disturbance responsible for the neuropathy is unknown. The pathogenesis of diabetic neuropathy probably will not be fully elucidated until considerable histologic material from living patients has been studied intensively. Anatomically, almost any part of the nervous system may be involved in diabetes, although the lesions most commonly recognized clinically are those of the peripheral nerves. The nervous system unit usually affected is the poorly myelinated, small caliber neuron in the peripheral nerve (1). This neuron is responsible for the mediation of pain and thermal sensibility. It also mediates autonomic functions.

Submitted Feb. 24, 1955.

For the purpose of discussion, the possible etiologic factors of diabetic neuropathy encountered most commonly in the literature are the following: A. Atherosclerosis; B. Vitamin deficiency; and C. Diabetes.

A. ATHEROSCLEROSIS

Peripheral atherosclerosis involving the small vasa nervorum, and producing an ischemic neuropathy, frequently has been regarded as the important etiologic agent in the production of diabetic neuropathy. Woltman and Wilder (2), in 1929, described the pathologic changes in the peripheral nerve in 10 cases of diabetes. They found that the most significant lesions are associated with marked thickening of the walls of the intraneural vessels. This vascular, or circulatory, explanation of the pathologic features in diabetic neuropathy has remained a leading thought and recently has been emphasized again by Broch and Klovsted (3) who state: "Vascular disease is of first importance in the

etiology of the neurologic complications of diabetes mellitus: arteriosclerotic changes in the vasa nervorum are an explanation of the peripheral nerve changes in diabetic neuropathy overlooked by many."

Dolger (4) and others likewise have thought that diabetic neuropathy is primarily a result of a vascular lesion. Weinstein and Dolger (5) concluded that extraocular muscle palsies in diabetes mellitus are best explained on the basis of small hemorrhages in individual nuclei of the third and sixth nerves. Dolger further postulates that minute vascular lesions in significant areas are responsible for the protean neurologic manifestations of diabetes, and that neuropathy is a sensitive indicator of the degree of vascular damage. On the basis of this concept this author points out that the nerve damage must be considered irreversible and improvement would not be expected with the use of vitamin preparations or with more rigid control of the diabetes. As pointed out elsewhere, this explanation is unacceptable to us (6). Fortuin and Wassing's (7) case 3 with cranial neuropathy was only 37 years old and, except for the very mild diabetes, was in perfect health. In two other of their cases, the palsy cleared up completely within a few weeks as so often happens. This would be a very unlikely occurrence had the lesion been caused by a hemorrhage into the corresponding nucleus. In our view the involvement in these cases is a peripheral nerve disturbance of varying number of fibers.

A simple review of the age of the patients who served as a nucleus for the deductions of Woltman and Wilder speaks against a vascular pathogenesis. Of the ten cases studied by these authors one was 49 years of age, four were between 50 and 60 years, two between 60 and 70, and three were over 70 years of age. Among the patients studied by Broch and Klövsted, 61 per cent were over 50 years of age with the more severe forms of neuropathy occurring in the older age groups.

Inasmuch as neurologic manifestations occur, in some instances, in the absence of significant atherosclerosis ischemia is not the whole answer. Neuropathic manifestations are frequently so widely disseminated as to preclude atherosclerosis as the etiologic factor on the basis of localization alone. Furthermore, cases in which the proximal portion of the lower extremity is predominantly affected, as in the frequently encountered femoral neuropathy (8), present strong evidence against a vascular genesis. One of the vital features of ischemic neuropathy is its localization in the distal areas.

In Jensen's study (9), the pulsation of the dorsalis pedis artery was retained in five out of eight patients with neuropathy. Rundles (10) found no significant degree of occlusive vascular disease in 80 percent of 125 cases of severe neuropathy. In 1941, Kauvar (11) published a statistical study of the relationship of atherosclerosis and neuropathy in diabetic and nondiabetic individuals. Twelve out of 65 diabetic patients with peripheral circulatory deficiency (18.5 per cent) had peripheral neuropathy. Only seven of 80 nondiabetic patients with peripheral circulatory deficiency (8 per cent) had neuropathy. Far from proving an ischemic genesis, as presented by Kauvar, these statistics can be interpreted to indicate that the higher incidence of neuropathy in the diabetic group with peripheral atherosclerosis is a result of an added factor—diabetes—superimposed upon the vascular disease of the extremities. Diabetic neuropathy often occurs in young patients without any circulatory abnormality; and, conversely, severe atherosclerosis in older diabetics is often *not* associated with neuropathy.

Rundles, Joslin (12) and others also suggest that the clinical facts cannot be reconciled to the viewpoint that vascular factors are important in the etiology of diabetic neuropathy. Occlusive arterial disease cannot be held responsible for its prevalently acute onset, frequent involvement of the visceral autonomic nerves and, most of all, the marked improvement or definite recovery when these patients are brought under diabetic control. As Joslin (12) points out, the fact "that diabetic neuropathy is often completely reversible also is evidence that the typical case of acute diabetic neuropathy has nothing to do with arteriosclerosis." Certainly, this ischemic theory does not hold up in patients who have no demonstrable atherosclerosis and in those who undergo complete recovery.

If the pitfall of attributing diabetic neuropathy to a deficient circulation is to be avoided the neurologic manifestations in diabetic patients have to be given more careful consideration. Although paresthesia, pain, ulceration, etc., may co-exist with arteriosclerosis obliterans, the presence of the latter does not exclude the possibility that the neuropathy may still be entirely neurogenic. Absent or sluggish tendon reflexes in the lower extremities afford valuable clues in identifying the inherent neurologic nature of the disorder.

Previous observations (8) also fail to show a correlation between neuropathy and vascular insufficiency of the lower limbs. That vascular impairment, from whatever cause, can lead to peripheral nerve lesions is beyond dispute. While this may be true in an occasional case, still, in our material, the incidence of ischemic neuropathy is extremely low in contrast to a high incidence of peripheral atherosclerosis (46 per cent) (13). In my opinion, the confusion as to the vascular genesis of diabetic neuropathy arises from the frequency with which peripheral atherosclerosis and neurologic manifestations both occur in diabetes. In other words, though sclerosis may be the direct cause of neuropathy in a few cases, in most instances it is merely a concurrent finding. In view of the high incidence of both peripheral atherosclerosis and neuropathy in diabetics, their chance coexistence, at least, must be acknowledged. Pure ischemic neuropathy does occur in some diabetics and should be recognized as such. The diagnosis of an ischemic neuropathy must be supported by the physical signs of circulatory inadequacy. That all cases of diabetic neuropathy arise from a primarily vascular process is most unlikely.

B. VITAMIN DEFICIENCY

A widespread notion that vitamin deficiencies are the cause of diabetic neuropathy calls for some comment. It is long established that, normally, carbohydrate is the principal foodstuff utilized in the metabolism of nerve tissue, and that at least three of the B vitamins are essential in the scheme of glucose metabolism. Thiamin, for example, not only is intimately associated with carbohydrate metabolism, but also plays an im-

portant role in maintaining the normal metabolism of nerve tissue. Inasmuch as the neuropathies of diabetes and beriberi may give rise to similar symptoms it was natural that vitamin B, should be given to patients with diabetic neuropathy. Because animals with avitaminosis may be restored to a nearly normal condition within a few hours by the administration of the vitamin, the neuropathy is certainly not due to a permanent lesion of the nervous system. Since such rapid improvement is due directly to the action of vitamin B, it appears that in the early stages neuropathy due to vitamin B deficiency is a chemical phenomenon.

Observation of 100 cases of diabetic neuropathy led Rudy and Epstein (14) to the conclusion that the nervous system damage was due to profound biochemical disturbances pointing to vitamin deficiency *not* attributable to poor dietary intake. In the absence of rapid response to vitamin administration, i. e., when there is no obvious improvement in the neuropathy over a three to four weeks period, one is inclined to conclude that there has been actual anatomic degeneration. It would seem that in vitamin deficiency damage to the nervous system is only functional at first, while in the presence of continued shortage of the vitamin the damage progresses to a permanent type of nerve degeneration.

The fact that some diabetics are deprived of bread, cereals and other food rich in vitamin B has been advanced as reason to add vitamins to the diets of patients with diabetic neuropathy, even by those who consider neuropathy only in part a vitamin deficiency. I am loath to admit that the demonstration of malnutrition in a diabetic patient is ample proof that neuropathy in such a patient is the result of malnutrition. Nevertheless in the hands of the average physician it has become routine to prescribe one or more of the B vitamins for diabetic neuropathy.

The published reports indicating a definite value of vitamin therapy for diabetic neuropathy, to date, are far from conclusive. Most of these papers have said little about concurrent diabetic control. In few of the case histories described are there evidences of stability before the institution of vitamin therapy. Diabetic patients are often given vitamin preparations while they are still improving under previously instituted dietary and insulin regimens and any further improvement is credited to the vitamin. In many patients weight is reduced to a more desirable level. Thus, it is always doubtful whether the improvement observed was due to the vitamins given or to continued regulation of the diabetes.

It is not inconceivable that thiamin deficiency neuropathy may be present coincidentally with true diabetic neuropathy. An occasional patient with neuropathy is apparently deficient in thiamin and, at the beginning, most of these are not aided by diabetic therapy. Certainly, diabetic patients with evidence of B_1 deficiency should receive adequate doses of the vitamin. On the other hand, notorious failure to reverse neurologic changes in many patients receiving huge doses of vitamins seems to invalidate the concept that any member of the B fraction is a responsible etiologic factor. On the basis of the evidence at hand I feel that, despite reportedly favorable results of Rudy and others, this vitamin should not be employed routinely for diabetic patients, with or without neuropathy.

C. DIABETES

Although neuropathy has been attributed to other causes, studies by Rundles (10), Joslin and his associates (12), ourselves (8), and others (15-17) on the detailed diabetic background of patients with neuropathy agree that most of the patients have had antecedent histories, usually of months' or years' duration, of neglected or uncontrolled diabetes. This has been universally true in groups of patients from the New England Deaconess Hospital reported by Root and Rogers (18), Jordan (19) (226 cases), and Bailey (20) (50 cases). In Epstein's (21) series, only eight patients developed neuropathy when the diabetes was well controlled. Definitely poor regulation was present in 29 cases, and in nine of these there was manifest acidosis at the onset of neuropathy. In a series of 74 patients with neuropathy among 150 diabetics, Bonkalo (22) stressed the high blood sugar level and the frequency of the severe type of diabetes with a special propensity for the development of ketosis. In a series of 113 cases, observed during the year 1950 at the New England Deaconess Hospital, 12 seemed under good control upon admission, but in no case could it be said that the neuropathy had begun at a time when diabetes was well controlled. The vast majority of our own cases of diabetic neuropathy have been associated with poor diabetic control (8).

While the patients with diabetic neuropathy have, on an average, higher blood sugar levels than those without neuropathy, hyperglycemia *per se* will not cause nerve lesions (22). Neuropathy cannot be correlated with the amount of glycosuria or the presence of acetone or diacetic acid in the urine. Besides, acidosis is more likely to be seen in younger individuals, so that one would expect to encounter a higher incidence of neuropathy in the younger age groups, when, as a matter of fact, the reverse is true. It is unlikely that glucose, acetone, oxybutyric acid, etc., produce these nerve changes.

Probably, references to hyperglycemia as an etiologic agent in diabetic neuropathy connotes simply the prevalence of high blood sugar in the uncontrolled diabetic patient. Lack of diabetic control is, of course, characterized clinically by an elevation of blood and urine sugar, in addition to weight loss and other diabetic symptoms and complications. While regulation of the diabetes seems, to date, to be the most important corrective factor in diabetic neuropathy, it is not the establishment of a normal blood sugar *per se* that is curative.

Lack of diabetic control is the most probable etiologic agent in diabetic neuropathy. The great frequency of neuropathy in diabetic patients compared to nondiabetic patients leaves a basis for the conviction that diabetes itself has a direct bearing in some way upon the etiology. It is evident that the symptoms of neuropathy begin at a time when the sugar in both the blood and urine is abnormal. Even after diabetes has existed for 15 years, those who maintain ideal control tend to have less evidence of neuropathic changes than those who are unable to keep good control. The conclusion is unavoidable that neuropathy results not from high blood sugar itself but has something to do with a specific toxic effect upon nerve tissue. Gregory and Lindley (23) offer the attractive theory that, with carbohydrate

deprivation, perhaps excessive oxidation of fat leads to demyelinization.

Although uncontrolled diabetes is the usual forerunner of the diabetic neuropathies, this is not always so. In fact, neuropathy has been observed in patients before the diabetes develops.

The neurologic abnormalities in diabetic neuropathy are degenerative in nature (demyelinization), although, as Gregory and Lindley point out, it is difficult to comprehend how the specific pathologic lesion can be a degenerative one in patients who recover rapidly.

Regardless of our paucity of knowledge concerning the precise etiologic factors in diabetic neuropathy there seems to be fairly general agreement that adequate control of the diabetes prevents these changes. Here is another instance where prevention is better than cure. Rundles (10) says that "therapeutic experience confirms the *diabetic etiology* of diabetic neuropathy and that successful treatment of diabetic neuropathy requires meticulous diabetic regulation while no other type of therapy has been of definite value, implying a definite relationship to the natural history of diabetes." In my personal experience the acute types of neuropathy are readily corrected by diabetic control.

CONCLUSIONS

Though vitamin deficiencies may co-exist with diabetic neuropathy, they are not essential to its production. The administration of thiamin, or other vitamins, without therapeutic control of diabetic metabolism, does not suffice to bring relief in true diabetic neuropathy. Unlike the latter, thiamin deficiency neuropathy yields promptly to specific vitamin therapy.

In spite of our ignorance of the etiology of diabetic neuropathy I agree with those authors who maintain that poor management of the diabetes is the important factor. My co-workers and I have observed numerous cases of diabetic neuropathy without clinical evidence of atherosclerosis, which indicates that diabetes *per se* plays the dominant role in the precipitation or aggravation of the neuropathy of diabetes. It is not the severity of the diabetes, but lack of control, which underlies neuropathy. In the final analysis the intimate mechanism by which diabetes causes neuropathy is not known. The cause probably lies in some, as yet, obscure metabolic change in nerve tissue incidental to uncontrolled diabetes.

Despite this lack of clear understanding of its mechanism, the management of diabetic neuropathy is hopeful. It is one complication of diabetes which can be prevented, or cured, provided meticulous diabetic regulation is instituted sufficiently early.

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ABSTRACTS ON NUTRITION

OTA, S. AND SHIBATA, M.: *Studies on the mechanism for sugar absorption by rabbit intestine.* Kyushu Memoirs of Med. Sci., 5, 2, Sept. 1954, 107.

The rate of absorption varies for different sugars in the following order—galactose, glucose, fructose, ribose, xylose and arabinose. All these sugars, except arabinose, are phosphorylated during absorption in the order of fructose, galactose, glucose, ribose and xylose. No intrahepatic circulation of phosphates during absorption of sugars was found. Sugar was esterified on the surface of the mucous membrane and left the mucosa in the form of free sugar. Most of the split inorganic phosphate remained in the mucous membrane for further phosphorylation of sugars about to be absorbed. The phosphates required for this purpose were supplied by the mucosa itself and not from the intestinal content or from the blood. The phosphorylation of fructose was caused by some unknown specific process different from that used in the case of glucose. Bile did not generally promote the turnover of phosphates in the mucosa, but it did accelerate the absorption of glucose and fructose and the turnover of phosphates in the case of these two sugars. Arabinose was absorbed by some physical process without being phosphorylated. Moniodoacetic acid inhibited not only the phosphorylation of sugars, but also the widespread phosphate metabolism, causing severe intestinal damage as a result.

BROCHNER-MORTENSEN, K., KRARUP, N. B., MEULENGRACHT, E. AND VIDEBAEK, A.: *Ineffectiveness of chicken anti-ulcer factors in the treatment of gastric and duodenal ulcer in man.* Brit. Med. J., Apr. 2, 1955, 88.

Ulcers in the gizzards of the chick can easily be prevented by inclusion in the diet of hog liver, calf's brain or certain extracts therefrom. A markedly effective prophylactic is obtained by combining a lipid extract and an aqueous extract of calf's brain. (The aqueous extract may be replaced by vitamin B_{12}). 82 randomly chosen patients with gastric or duodenal ulcer were treated with "anti-gizzard ulcer factors" (ether extract of calf's brain plus vitamin B_{12}). Seventy similarly chosen control patients were subjected to the same regime with placebos substituted for the anti-gizzard ulcer factors. Results were based on clinical and x-ray follow-ups. The experimental and the control groups did not differ at all in their response to treatment. The "anti-gizzard ulcer factors" were thus of no value in the treatment of gastric and duodenal ulcer in man.

HIRATA, Y.: *Studies on experimental diabetes.* Kyushu Memoirs of Med. Sci., 5, 2, Sept. 1954, 95.

Hirata noted that after administration of alloxan, the serum potassium concentration of rabbits increased with the initial hyperglycemia and decreased in the hypoglycemic phase. He proved experimentally in rats that sodium thiolactic acid prevented the development of alloxan diabetes. The reaction with dithizone with zinc was prevented by solium thiolactic acid or BAL, but not by sodium thiosulfate. Administration of sodium thiolactic acid or BAL before the injection of dithizone prevented the development of dithizone diabetes, but sodium thiosulfate had no such preventive action.

GANDEVIA, B. AND HOSSACK, D.: *Tongue appearance and serum albumin level in the assessment of nutritional status with reference to the effects of a protein-rich diet.* Med. J. Australia, Mar. 5, 1955, 344.

A relationship was demonstrated by Bolton (M. J. Australia 1955, 1, 10) between the sequence of changes in the tongue leading to complete atrophy and the dietary intake of meat and eggs. Five grades of tongue changes were recognized, the first abnormal change being edema of the tongue, then the loss of papillae leading to the fifth change, viz., a smooth shiny, completely atrophic tongue. In a series of 24 students living at home, a mean grade of tongue change was less and the mean serum albumin higher than in a series of 16 students living in institutions. After 2 weeks on a protein rich diet, the "institution" students showed improvement in mean tongue grade and serum albumin level, the values becoming identical with those for the "home" students. Statistical analysis indicates that the mathematical combination of tongue grade and serum albumin content is a sensitive index of group nutritional status in respect to protein,—a finding that has wide practical application in studies of human nutrition.

MACK, P. B., DIXON, M. S. WITH TECHNICAL ASSISTANCE OF BAUR, M., AMMERMAN, E. H. AND THOMAS, M.: *A study of the relation between ingestion of frozen orange juice and resistance to fatigue.* Am. Pract. & Dig. Treat., 6, 4, Apr. 1955, 584.

The use of frozen orange juice between meals gave favorable effects in endurance tests, in pulse-ratio (step tests) and in speed-accuracy tests in both children and adults. Although the glucose content of orange juice was considered chiefly responsible for these effects, the presence of ascorbic acid and the carotenes undoubtedly played a part.

TRÉMOLIÈRES, J., MOSSÉ, A., LYON, L., PASCHOUD, J. AND SAUTIER, C.: *Metabolic Effects of High-protein Low-sodium Diets in Liver Cirrhosis.* "La Presse Médicale," Paris No. 87, 29 Dec. 1954.

A study of nitrogen, sodium and potassium balances in cases of alcoholic ascitic cirrhosis of the liver led to the following observation. The 24 hour diet ranged between 100 to 250 g in protein, 15 to 20 mEq of sodium and 50 g of lipids.

1) The most striking observation was the intensity and the long duration of nitrogen retention. Nitrogen balances were positive between + 9 to+20 g of nitrogen a day. This anabolic state lasted more than two months. Fecal nitrogen was normal. With this diet,

the protein level of the ascitic fluid raised. These cirrhoses behaved like severe protein deficiencies.

2) Urinary sodium is below 1 mEq 24h and fecal sodium is normal during acute phases of the disease. The low sodium diet is unable to cure ascites but it slows to a great extent its speed of reproduction. With a urinary sodium of more than 10 mEq, it is not necessary to control Na intake, patients being normally able to excrete it.

The correlative studies of the variations of the weights in the patient and those calculated from nitrogen and sodium balances show that important changes in sodium distribution inside the body must interfere. The actual weight of the patient correlates very well with that of the sodium balances alone.

These diets contribute to change food habits as regards alcohol, the disease appearing when the food intake is restricted and alcohol increased.

Guy Albot

WAIFE, S. O.: *Glucagon.* Illinois Jour. Med., 107, 2, Feb. 1955, 81.

The first insulins used produced a transient hyperglycemia, due to a hypothetical contaminent for which the term "glucagon" was coined. Following the crystallization of insulin by Abel, no hyperglycemic effect was noted from this purified insulin. In 1953, Staub at the Lilly Research Laboratories isolated crystals of glucagon. It is a protein of low molecular weight having no chemical resemblance to insulin, although the crystals do resemble those of insulin. Glucagon is presumably produced by the alpha cells of the islets. The sole function of glucagon is to act on the liver glycogen alone. It has no action on muscle glycogen. Fortunately the presence of glucagon does not interfere with the assay of insulin. There is probably less than 3 percent glucagon in insulin.

GRAHAM, J. W.: *Hypoproteinosis in children.* Northwest Med., 54, 1, Jan. 1955, 40.

For years, Graham has noticed a familiar symptom complex in children, the symptoms of which are severe dental caries, sub-par gingiva, poor appetite, irritability and repeated upper respiratory infections. Always this syndrome was associated with diet which, though adequate in vitamins, was deficient in proteins. Generally the diet consists of milk and carbohydrate foods, taken in large quantities with a neglect for meat, eggs and other proteins. Considerable education of the parents of these children is needed to supply an adequate protein diet. Sometimes milk has to be given up to make room for meat. Once the change has been made, the results are good.

EDITORIAL

THE BLIND SPOT IN THE BILE DUCT

Glisson (1690) and Vater (1720) described the papilla at the termination for the bile duct. Oddi (1895) and Opie (1904) described an ampulla for the termination to the bile and pancreatic ducts. Robson (1905) described variations in the union at the terminations for the pancreatic and bile ducts. Dardinski (1936), Boyden (1939) and Sterling (1947) clarified the anatomical characteristics to the *pars intestinalis* of the common bile and pancreatic ducts.

Anatomists and pathologists now recognize that the termination to the ducts at the *papilla* is through a complex sphincter; and that the ampulla for the bile duct is present only in the embryo. None-the-less, much dissection, maceration, compression and injection have been applied to the papilla without doing more than providing an insecure basis for the promulgation of myriad theses.

This occurs because the termination for the bile duct is a blind spot clinically and surgically. Often, only indirect evidence is available concerning the papilla and its function and in many instances there is confusion and inconsistency regarding the distal segments of the ducts.

An example of inconsistency is that the terms of "papilla" and "ampulla" are interchanged. Etymologic analysis indicates that an elevation or swelling (the papilla) such as a nipple, should not be confused with a dilated end of a vessel, canal, or duct (the ampulla) particularly when the former means a "mass," and the latter a "space." Hence, the so-called "carcinoma of the ampulla" (or "tumor of a space") is misleading. The term "ampulla" does not ordinarily apply to the termination for the bile duct.

The primary function of the biliary tract is transportation of bile from the liver to the duodenum. This pipeline includes a "surge chamber" (represented by the gall bladder) permitting both storage and availability. The duct has a "nozzle" at its termination, which increases the flow of bile to jet-stream velocity. These facts agree with physical principles of flow through a pipe and with similar laws of hydraulics.

The diameter of the common bile duct lumen is normally less than one centimeter. Its termination at the papilla of Vater is like a funnel and the diameter of its orifice is usually one to two millimeters.

The pancreatic and common bile ducts generally maintain their identity through the papilla. Careful examination of intact, cleared specimens after filling the ducts with opaque dyes has demonstrated that in 80% of specimens the ducts' terminations are absolutely separated or there is a shallow common channel for one or two millimeters. In 14% of cases the common channel for pancreatic and common bile ducts is in the distal one-third of the papilla. In only 6% does the common channel for the ducts traverse more than half of the papilla, and only in these does the occasional "ampulla" appear.

Furthermore, consideration of the disposition and character of the papillary sphincter indicates that the presence of interductal reflux depends upon the exist-

ence of a common channel for the bile and pancreatic ducts for a distance greater than half the length of the papilla.

Only certain abnormalities of the papilla are reflected in the extraduodenal common bile duct. The most frequent change in the bile ducts is that of dilatation. The common bile duct is abnormal when greater than one centimeter in diameter.

It is important to relate the location of interductal reflux to the position of stone impaction. Usually the calculus is lodged at the distal end of the extraduodenal common bile duct. Because a mass of tissue is present at the papilla to act as an obstacle, the stone within the bile duct is propelled by increases of intracholedochal pressure to areas of least resistance. These are toward the duodenal wall or to the pancreas and its duct. A diverticulum, which is formed, can be perforated and an internal choledochal fistula result. Abnormal interductal reflux can thereby be produced through such traumatic and inflammatory choledochal-pancreatic fistulae. Pancreatitis is present in such cases.

Surgical and necropsy study of this area is very difficult. Post-mortem autolysis of the papillary region is increased by normal intestinal enzymes. Our data, therefore, is still incomplete.

One of the first things to be done is to balance unseemly theorizing by the use of correct terminology for anatomical structures at the terminations for the bile duct.

It is strongly urged, therefore, that the termination for the bile duct be indicated as the sphincter, or papilla.

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BOOK REVIEWS

PRACTICAL MANUAL OF PROCTOLOGY. René B. Henry and G. B. E. Simonetti. J-B. Bailliere et Fils, 19, Rue Hautefeuille, Paris VI.

In something over 300 pages the distinguished authors present in succinct form, practically all that it is necessary to know, in order to diagnose and treat diseases of the anus and rectum. The book is beautifully illustrated with a generous sprinkling of color plates. Ambulant proctology is becoming popular in France. A considerable portion of the space is devoted to various refinements of surgical technique. Extensive bibliographies follow each section. The book should be translated into English.

LES MALADIES DE L'ANUS ET DU CANAL ANAL. Pierre Hillemand, Alfred Bensaude, and Jean Loygue. Masson et Cie, 120 Blvd. Saint Germain, Paris 6, 3400 francs.

For the first time in French medical literature a complete work on the anus and the anal canal is presented. It is one which encompasses all the diseases occurring in this region from hemorrhoids to carcinoma. The authors bring to bear on the subject not only rectal but general gastroenterological concepts and the dermatological knowledge which often is essential. The text contains many color illustrations.

METHODS FOR EVALUATION OF NUTRITIONAL ADEQUACY AND STATUS. Committee on Foods, Advisory Board on Quartermaster Research and Development. Dept. of the Army, Office of the Quartermaster General. Copies available at the Quartermaster Food and Container Institute for the Armed Forces, 1819 W. Pershing Road, Chicago 9, Ill.

Many contributors have produced an excellent book which aims at an evaluation of the dietary for military personnel under varying external conditions, as well as the perfecting of methods for knowing the nutritional status of the individual soldier. The protein, vitamin and mineral requirements are dealt with at length. Military rations have been evaluated both by animal and human experiments. The problems involved in feeding subjugated populations receive attention. The potential offered by the new field of measurement of body compartments as an index of nutriture is reported enthusiastically in the round table discussion which forms the last chapter. Copies are available for all physicians interested.

MANAGEMENT OF ADDICTIONS. Edited by Edward Podolski, M. D. Philosophic Library, New York. 1955. $7.50.

A large number of authorities have contributed, in this volume, to the distressing problems concerned with alcohol and drug addictions. Unfortunately, a reading of the book leaves one with a sense of what we do *not* know about the causes of addictions and about scientific methods of treatment. It is true that the physical effects of alcoholism can now be satisfactorily treated. This, however, leaves the psychological aspects largely uninfluenced. As Podolski admits in his preface, A. A. has become the best form of treatment for chronic alcoholism. The book is decidedly worth studying for all who are interested in this baffling and pathetic aspect of medicine.

PATHOLOGY. Peter A. Herbut, M. D. Lea and Febiger, Philadelphia 6, Pa. 1955, $16.00.

The present volume, considering its size (1230 pages) and its profusion of half-tone etchings, with 6 color plates, is cheap at the price at which it is offered, especially in view of the fact that Herbut has written a somewhat "different" kind of pathology. There is a close unity between the clinical events and the post-mortem or biopsy appearances. Of course, the main thesis concerns disease processes as they are reflected in gross specimens and microscopic views. There is a separate chapter on autopsies and how to do them. The chapters on the lower urinary tract and on the male and female generative systems are probably more complete than can be found in text-books on pathology. We highly recommend the volume to all practicing physicians and students.

AMER. JOUR. DIG. DIS.

GENERAL ABSTRACTS OF CURRENT LITERATURE

WEINBERG, A. AND WERNER, W. E. F.: *Bonadoxin: a new effective oral therapy for hyperemesis gravidarum.* Amer. Pract. & Dig. Treat., 6, 4, Apr. 1955, 580.

The authors report that a new antihistamine, meclizine hydrochloride, combined with pyridoxine in a suitable oral dosage has a prolonged favorable effect on the great majority of cases of nausea and vomiting of pregnancy. It is made under the trade name of Bonadoxin. (J. B. Roerig and Company).

RUNYEON, W. K., HOERR, S. O. AND HAZARD, J. B.: *Hypertrophic pyloric stenosis in the adult. (Discussion of etiology and report of a case).* Cleveland Clinic Quart., 22, 2, April 1955, 76.

About 80 percent of adults having hypertrophic pyloric stenosis are males, as in the infantile group. Repeated bouts of epigastric pain and vomiting are common, and the average duration of symptoms is 10 years. A high incidence of co-existent ulcer or gastritis generally is reported. Whether the disease in adults actually dates from infancy is uncertain, but probable because so often a history of gastric complaints dating from childhood is elicited. Hypertrophy may play some role in the production of gastric ulcers. A case in a 65 year old man is reported in detail. Because of the virtual impossibility of making the differential diagnosis between hypertrophic pyloric stenosis and prepyloric cancer prior to tissue section, subtotal gastrectomy is the procedure recommended.

WISE, S. P., III, DOENGES, J. P., HUNGATE, J. L. AND VIELHABER, D. P.: *Peptic ulcer in military personnel: management in the outpatient clinic.* U. S. Armed Forces Med. Jour., 6, 4, April 1955, 500.

A satisfactory outpatient treatment program for 102 enlisted men with peptic ulcer was established at the U. S. Army Hospital, Fort Jackson, S. C. Treatment consisted of the use of aluminum hydroxide with magnesium trisilicate taken 30 minutes after each meal and at bedtime; Banthine bromide 50 mg. taken 30 minutes before each meal and 100 mg. at bedtime; one-half pint of milk taken 5 times a day in addition to the regular ration. Emotional problems were dealt with by the medical social work officer. Of 91 patients who could be followed, 81.3 percent were rated satisfactory for service while 18.7 percent were unsatisfactory at the end of a 7 months' period. Hospitalization was used only for complications. The vast majority greatly improved and made a satisfactory adjustment to the Service. It would appear that the outpatient treatment of patients with peptic ulcer in the Army is the preferable approach to this problem.

OFFLERBAUGH, J. K. AND COLE, H. A.: *Intragastric gallstone.* Radiology, 64, 4, Apr. 1955, 581.

A case is presented in which a large gallstone was demonstrated radiologically in the stomach and was subsequently removed. It could be established that this very large stone had passed through a cholecystoduodenal fistula and thence through the pylorus into the stomach. A previous study had revealed the stone in the gallbladder. In the literature mention is made of gallstones in the stomach, but this is the first time such a stone has been demonstrated by x-ray.

SEABURY, J. H.: *Antibiotics in gastroenterology.* Amer. Pract. & Dig. Treat., 6, 4, April 1955, 533.

Seabury writes at some length on the favorable and unfavorable effects of antibiotics, particularly as they may affect the bacterial population of the gut. Chloramphenicol wipes out typhoid fever and Seabury, who sees 25 cases a year in New Orleans, has noted no adverse effects from its use. More Salmonella infections probably respond to either oxytetracycline or chloramphenicol than to other available antibiotics. Oral neomycin has proved of value in the control of infantile diarrheas due to coliform organisms. In *escherichia cholangitis,* neomycin parenterally, though toxic, exerts a very favorable effect. In staphylococcal food poisoning, erythromycin should always be given. In intestinal amebiasis, Seabury prefers fumagillin as the antibiotic of choice. The advisability of using antibiotics to sterilize the colon prior to abdominal surgery is open to question because before the era of antibiotics, few instances of peritonitis followed good surgery, and further because there is always the danger of moniliasis or even acute membranous enterocolitis. It must also be remembered that antibiotics interfere with the "balance" existing among different species of the intestinal flora and between them and the mucosa of the bowel. Many antibiotics are irritating. At times allergic reactions may occur. In non-specific ulcerative colitis, it is doubtful if antibiotics are of any value except to tide patients over crises.

YOUNG, B. R.: *Roentgen examination of the acute abdomen.* Radiology, 64, 4, April 1955, 483.

Plain scout films of the abdomen frequently are highly informative with respect to the nature and site of an acute process within the abdomen. Occasionally contrast media may be required. Thus, mechanical, vascular and paralytic ileus; volvulus; intussusception; external and internal hernias; perforation of a hollow viscus with resultant gas in the peritoneal or retroperitoneal speaces; calculous disease and inflammatory, cystic and neoplastic enlargements of the gallbladder, pancreas and kidney; appendiceal, pelvic, and subdiaphragmatic abscesses and finally rupture of kidney or spleen are conditions which may be unmistakably diagnosed. The article is profusely illustrated with x-ray films.

DAGRADI, A., SANDERS, D. AND STEMPIEN, S. J.: *The sources of upper gastrointestinal bleeding in liver cirrhosis.* Ann. Int. Med., 42, 4, April 1955, 852.

From a careful study of 121 cases of cirrhosis of the liver, it became apparent that the commonest sources

of upper gastrointestinal bleeding in hepatic cirrhosis are esophageal varices, hemorrhagic gastritis and duodenal ulcer. Hemorrhagic gastritis ranks almost equally with varices as a frequent cause of bleeding. The differential diagnosis of bleeding in cirrhosis must include all of the bleeding lesions common to noncirrhotic patients in addition to esophageal and gastric varices. Esophagoscopy and gastroscopy are important adjuncts in diagnosis.

FRAENKEL, G. J. AND TRUELOVE, S. C.: *Hematemesis: with special reference to peptic ulcer.* Brit. Med. J., Apr. 23, 1955, 999.

From 1948 to 1952, at the Radcliffe Infirmary, Oxford, 540 cases of hematemesis were admitted as emergencies. In 17 out of every 20 cases, bleeding was due to peptic ulcer. The total death rate was 8.3 percent. For 377 patients with definite peptic ulcer, the rate was 5.6 percent. Among the ulcer patients 1 in 3 suffered from continued or recurrent bleeding after admission to hospital. The chance of recurrent bleeding was not influenced by age, length of ulcer history, or history of past bleeding. In the peptic ulcer group 7 out of every 10 made a good recovery from bleeding on medical management. One in every 6 had an emerency partial gastrectomy for bleeding, with a mortality rate of 9.2 percent. Partial gastrectomy should perhaps always be done when there is continuous or recurring hemorrhage.

JONES, H. L., CASSIS, G., FLOYD, T. M. AND MANSOUR, N. S.: *Amebiasis: controlled linear studies on nondysenteric and mild hepatic forms in Egyptians.* Ann. Int. Med., 42, 4, Apr. 1955, 763.

Ten of nineteen apparently healthy Egyptians showed varying frequencies and densities of large and small races of *E. histolytica.* Five subjects showed only small race amebae in their stools. The mixed group had more abnormalities of their stools than in the case of the small race group. Vioform, followed by carbarsone was used in treatment. When hepatic involvement seemed apparent, chloroquine diphosphate was also used. Apparently the small race of amebae has mild pathogenicity. Apparently healthy carriers of either race may have mild symptoms and signs of amebiasis if followed over long enough a period.

WILLARD, J. H.: *The chief medical problem in military medicine: peptic ulcer—medical aspects.* Military Medicine, March 1955, 179.

At the present time in the forces in Europe, peptic ulcer represents as high as 10 percent of medical admission to hospitals; and infectious hepatitis is now of secondary importance. Radiologists in the European Theater are finding as high as 60 percent positive findings of ulcer in routine G. I. x-rays as compared with about 20 percent in the U.S.A. The complications (perforation, hemorrhage, obstruction) occur in about 10 percent. Hospital admission rates for ulcer among soldiers are higher among troops in training or in inactive areas than among troops actually engaged in combat. The psychiatric aspects of ulcer are of prime importance, and the mental factors are related to poor motivation among soldiers and unsatisfactory integration into the service. The incidence of ulcer is much higher in persons with less than 4 years' service than in those with more than 10 years' service. The prognosis of ulcer in the services is not good because of a desire to be returned to civilian life. Willard recommends all the accepted methods of treatment used in civilian life, but the response is not so early. An individualized educational approach is needed, but this is almost impossible in the armed services. Probably a soldier with ulcer who has less than 6 years of service has no place in the Regular Army. If a man has more than 12 years' service, he should be permitted to remain in the army if he so desires, particularly because of the valuable knowledge he has accumulated. A commission should be appointed for the purpose of more accurately evaluating all the facts connected with this very serious hazard.

POLLARD, H. M.: *Hemorrhage from the upper gastrointestinal tract.* Illinois Med. J., 107, Jan. 1955, 1.

Pollard likes to determine the site of bleeding early in the case, and does not hesitate to use esophagoscopy, gastroscopy and barium meal x-rays without compression. The patient with sclerosed vessels requires special watching. Morphine is not advisable. Early feeding is valuable. Transfusions are valuable, but there is reason to believe that the massive rapid transfusion is not indicated, and that following some delay small transfusions by the drip technique are more desirable. Emergency surgery, in the presence of recurrent or continuous bleeding, should be given serious consideration in persons over 60 years of age.

RUMORE, P. C.: *External pancreatic fistulas.* Illinois Med. J., 107, 1, Jan. 1955, 24.

External pancreatic fistula results from external trauma or injury during surgery, especially marsupialization of a pancreatic cyst. Some fistulas close spontaneously. When this is not the case, the fistula is dissected down to the pancreas and excised along with a portion of pancreas, in cases where the tail is involved. Such cases offer a good chance to study the external secretion of the pancreas. Banthine is the drug of choice in reducing the flow of pancreatic juice, and thus leading to healing, but it has the one disadvantage of rendering the juice thick so that it may plug the cannula which has been inserted in the external opening of the fistula.

RATNOFF, O. D. AND PATEK, A. J., JR.: *Postnecrotic cirrhosis of the liver: a study of 45 cases.* Jour. Chronic Diseases, 1, 3, March 1955, 266.

The natural history in 45 proved cases of postnecrotic cirrhosis of the liver has been reviewed and compared with that of Laennec's cirrhosis. This type of chronic liver disease is characterized by necrosis of liver cells, regenerating nodules of hepatic tissue, the presence of large bands of connective tissue coursing irregularly though the liver, and, in some areas, preservation of the normal hepatic architecture.

Laennec's cirrhosis occurs at least twice as frequently in males as in females. In contrast, 60 per cent of our 45 patients with postnecrotic cirrhosis were female. The disease appears at any age, and is relatively more frequent in younger patients than is Laennec's cirrhosis. Since postnecrotic cirrhosis may follow hepatic injury due to several seemingly un-

related causes, the wide age distribution and relatively equal sex incidence are not surprising.

The most common pathogenetic factor in the present series appeared to be acute hepatitis. The parenchymal injury in acute hepatitis is usually followed by complete healing. In a few cases, the disorder is fatal. In another small group, the illness assumes a progressive or intermittent course in which cirrhosis may appear. In most instances, this cirrhosis is of the postnecrotic variety. In 12 cases in the present series, the patient's illness began as if it were an acute hepatitis, which then failed to heal. Six other patients had a history of an attack of acute hepatitis five to twelve years before the clinical onset of cirrhosis and were distinguished from this first group only by the latent period between the first episode of jaundice and subsequent symptoms. It must be emphasized that no proof was obtained that any of these 18 cases was the result of infection with the virus of infectious hepatitis.

Postnecrotic cirrhosis has also been reported to result from hepatic damage due to a number of chemical agents, including trinitrotoluol, arsenic, phosphorus, chloroform, carbon tetrachloride, trichlorethylene, camphor, dinitrobenzene, naphthalene, and cinchophen. In the present series 4 patients had been exposed to hepatotoxic agents, and another 4 had been treated for syphilis with parenteral injections of arsenical compounds. Twenty-nine per cent of the patients in the present series admitted the prolonged consumption of alcoholic beverages in the years preceding their illness. Whether postnecrotic cirrhosis in these alcoholic patients was related to concomitant nutritional deficiency or whether they were more susceptible to other hepatotoxic chemical or infectious agents was not possible to determine. It is noteworthy that in 12 of the 45 patients it was impossible to discover any possible pathogenetic or etiological agent.

At the onset the symptoms of postnecrotic cirrhosis in 12 of the 45 patients were similar to those of acute hepatitis. This is decidedly different from Laennec's cirrhosis, in which such a dramatic onset is unusual. In the other 33 patients, the disease appeared insidiously and the initial symptomatology did not suggest the type of cirrhosis present. Abdominal pain or distress was present in a great majority of the patients, and symptoms referable to the gastrointestinal tract seemed more prominent than in Laennec's cirrhosis. Hematemesis occurred in one-third of the patients; if the patient survived the first hemorrhage he invariably bled again. Bleeding tendencies in the form of epistaxis, gingival bleeding, and purpura were frequent.

The physical signs of postnecrotic cirrhosis were similar to those of Laennec's cirrhosis. However, malnutrition was often much less conspicuous; one-third of the patients were described as well nourished. Jaundice was an early and often persistent sign. In many patients, transient increases in the intensity of the jaundice were associated with the return of symptoms suggestive of acute hepatitis. In the jaundiced patient, the lower serum cholesterol and serum alkaline phosphatase activity helped to distinguish postnecrotic from primary biliary cirrhosis. Ascites was a common sign which appeared earlier during the clinical course in alcoholic than in nonalcoholic patients. Other frequent signs were fever, hydrothorax, peripheral edema, and enlargement of the liver and spleen; at autopsy the weight of the liver averaged less than in Laennec's cirrhosis.

Of interest was the great frequency of positive cephalin cholesterol flocculation and thymol turbidity tests. A few patients had extreme hyperglobulinemia, a useful diagnostic aid.

Postnecrotic cirrhosis is occasionally found at autopsy in patients whose clinical course gives no hint of the possibility of liver disease. For this reason, it seems likely that it may sometimes be compatible with an otherwise normal life. Once symptoms have appeared, however, the prognosis is poor. In this particular series, one-third of the patients died within one year of the first symptom, and only one-quarter survived five years. The most frequent causes of death do not differ from those of other types of cirrhosis—cholemia, gastrointestinal hemorrhage, and infection. Although the disease appears to wax and wane, it is almost invariably fatal, and present therapy seems to be without effect. Occasionally, carcinoma of the liver complicates postnecrotic cirrhosis. Conversely, a number of reports have emphasized that the cirrhosis observed in patients with carcinoma of the liver is more frequently postnecrotic than one would expect.

There are many gaps in our knowledge about this disease. (a) It is still uncertain whether it can be the result of viral hepatitis, although this appears to be the case in a sizable number of patients. If it is, then some additional factor would seem to be involved, since almost all patients with viral hepatitis recover. Whether host or environmental factors or both determine the outcome is not known, although the occurrence of postnecrotic cirrhosis does not seem to be related to the severity of the initial hepatitis. (b) Its pathogenesis is not understood. Does it develop very quickly, as seems to be the case under some experimental conditions, and then remain latent for a period of time until symptoms appear, or do the anatomic changes develop slowly over a period of years? (c) It is not clear whether human postnecrotic cirrhosis can be caused by nutritional deficiencies, as is the case in experimental animals, or whether nutritional deficiencies will potentiate a lesion resulting from infectious or toxic damage. Finally, an effective therapeutic program for patients with postnecrotic cirrhosis is yet to be devised.

CASS, M. H., ROBSON, B. AND RUNDLE, F. F.: *Electrolyte losses with biliary fistula: the post-choledochostomy acidotic syndrome.* Med. J. Australia, Feb. 5, 1955, 165.

Measured over 5 day periods after operation, the electrolyte and water losses from a biliary fistula are of the same order as those from continuous gastric aspiration. With the uncorrected loss of biliary electrolyte, sodium is lost from the body fluids in excess of chloride. Base deficiency with acidosis results, contrasting with the chloride deficiency and alkalosis of uncorrected gastric loss. Thus a syndrome, here termed the post-choledochostomy acidotic syndrome, is described. Treatment presents no problem. Awareness of the possibility of its existence in the stuporous, failing patient is all that is needed. Biochemical confirmation is obtained in the low urine chloride excretion and the low serum sodium and chloride content, and carbon

dioxide combining power, together with a raised blood urea level. Correction of the deficit by oral or intravenous sodium chloride characteristically produces a dramatic improvement in mental and physical status.

BROWNE, F. S.: *Benign ulcer of the greater curvature of the stomach.* Amer. J. Roentgen., Rad. Ther. and Nuc. Med., 75, 3, March 1955, 398.

Browne presents an interesting case of a large ulcer situated on the greater curvature of the fundus of the stomach. It had all the accepted characteristics of a malignant ulcer but microscopic examination revealed a benign peptic ulcer. The patient had lost 15 pounds, had no free hydrochloric acid, and low total acidity. The decrease noted in the size of the ulcer following 10 days of medical treatment was confusing. A total gastrectomy was done.

HAEDICKE, T. A. AND GONZALEZ, J.: *Inverted duodenum.* Amer. J. Roentgen., Rad. Ther. and Nuc. Med., 75, 3, March 1955, 401.

A case of inverted duodenum is presented, bringing the total number of cases in the literature to 57. The second and third portions of the duodenum turned up and then over to the left side. The symptoms were similar to those of peptic ulcer and the patient responded to medical ulcer therapy. In some cases of inverted duodenum, surgery is needed. The diagnosis usually is made by x-ray.

GROULADE, J., TIZZANI, R. J. AND DRUFOVKA, B.: *A Quantitative Study by Microelectrophoresis on Paper of Serum Proteins in Diseases of the Liver.* La Presse Medicale, No. 65, 6, Oct. 1954. pp. 1349-1351.

The separation has been obtained using an original machine built in the laboratory, on Schleicher and Schull paper 2043 a (Veronal Buffer, pH 8, 6, ionic strength 0,1) in seven hours (6-5 volts/cm; 0-25 m A/cm) or thirteen hours (4 volts/cm, 0-12 m A/cm). The same weight of proteins has been put on the paper with variations of volume (12 mm3 with normal serum). The quantitative measure is made after the coloration by amidoschwartz 10 B and study of densitometry according to Grassman's and Hannig's method.

35 normal sera had the following percents (with standard deviation), Albumin: 58,6 ± 3 — Alpha 1 : 3,4 ± 0,9 — Alpha 2 : 7,5 ± 1,5 Beta : 12,5 ± 1,6 — Gamma : 18 ± 2,8.

Average rate of proteins (PHILIPS and Van SLYKE) 72 g/l ± 4.

In ethylic intoxication 199 sera and 15 ascitic fluids have been examined. The mean of results have been plotted into graphics showing the variation of per cent of the beta and gamma globulins in relation with that of albumin, of the weights of the beta and gamma globulins in relation with the proteinemia and finally of the per cent of albumins in relation with all the other fractions. The patients are divided into three groups:

1) At the beginning of the intoxication, a slight decrease of the albumin with an increase of the globulins (especially alpha 2) : stage of steatosis, with a frequent association of neuro-psychical signs.

2) At a more serious stage (hepatomegalia, varicosity of the cheeks) the fall of the albumins is better marked, all the globulins increase and some intermediate beta and gamma fractions appear. The proteinemia is important. It is the precirrhosis.

3) When the cirrhosis has been confirmed, the hepatic insufficiency shows itself in the progressive decrease of albumins. The alpha 2 come back to normal rates or increases (interference of infectious phenomena). The beta and gamma globulins largely increase and it is very difficult to separate them. The proteinemia which is most of the time high can go beyond 85 g (but it sometimes goes down).

4) A group has been studied separately because of the seriousness of the clinical signs given by 8 ascitic patients whose proteinemia is less then 62 g/l. The rate of albumins is most of the time inferior to 30%, that of the alpha 2 often inferior to 6%. The whole formed by beta and gamma reaches 60%.

Two examples (one with aggravation, the other with amelioration) show the parallelism between the electrophoretic signs and the evolution.

5) 15 ascitic liquids compared to the corresponding sera show the fall of proteinemia, the greater concentration of the albumin and of the alpha 2 globulins in the ascitic liquids whereas the other fractions become smaller.

From a brief confrontation with the histologic data it may be noted after HARTMAN and FAUVERT that electrophoresis informs us on the state of the epithelial tissue (albumins) and of the connective tissue (beta-gamma and intermediate fractions). The authors add to it an evaluation of the intensity of the toxical aggression at the beginning and later on, of the interference of infectious phenomena (alpha 2); the alpha 1 globulins appear in relation with phenomena of histolysis.

In a case of splenogenous cirrhosis, there is a marked decrease of albumins and an elective increase of the gamma globulin with hyperproteinemia.

Viral hepatitis offers the same characteristics but the gamma hyperglobulinemia is the translation of the hepatitis.

A mild icterus (5 cases) is characterized by a marked increase of the beta fraction and the absence of hepatitis —gamma are normal.

The averages in 16 obstructive jaundice cases has given the following per cent: Albumin 43,7 — Alpha 1: 6,4 — Alpha 2: 13 — Beta: 16,5 — Gamma: 20,3.

The first three globulins especially increase, the fraction alpha 2 is either in relation with the histolysis (epithelial tumor) or with the infection of vesicle. In the first case, there is an hypoproteinemia, in the second an hyperproteinemia.

In two metastatic carcinoma the increase was only on the alpha 2 (epithelial cancer) or on the gamma (metastasis of a melanotic cancer).

Guy Albot

AMER. JOUR. DIG. DIS.

CLINICAL AND PHYSIOLOGICAL EVALUATION OF SEVERAL ORALLY EFFECTIVE BRONCHODILATORS*

Hollis G. Boren, Demitri J. George, and Carroll A. Handley (V. A. Hospital, Houston, and Baylor University Medical School)

Presented at the National Tuberculosis Association Meeting, Milwaukee, Wisconsin

Three N-substituted arterenol derivatives have been studied in reference to their toxicity and bronchodilator properties following oral administration. These drugs seem to be free from significant toxic effects even though used for prolonged maintenance dosage.

Ventilation was improved by both N-(2(1-p-methoxyphenylisopropyl) norepinephrine hydrochloride and N-(2-(3,4 methylenedioxyphenylisopropyl) norepinephrine hydrochloride as indicated by subjective response and moderate increase in vital capacity. The latter drug seems preferable to use as it has less incidence of palpitation and tachycardia. Study by use of timed vital capacity, flowmeter tracings, and nitrogen washout gave no additional information.

To understand more completely the changes that occur following drug administration, it has been essential to use a simultaneous measurement of intraesophageal pressure and its associated volume and flow changes. Use of the method in normal persons has allowed criteria for increased airway resistance to be set up for the pressure volume breathing loops and a method of analyzing the loops is described.

Complete mechanical studies of breathing have been done in 36 instances, allowing evaluation of other drugs of the N-substituted arterenol series and showing, in addition, that N-(2(phenylisopropyl)) norepinephrine hydrochloride is effective in reducing resistance to airflow. Changes in resistance to airflow have been studied in a few instances following nebulized N-(2-(3,4 methylenedioxyphenylisopropyl) norepinephrine hydrochloride. These studies have indicated the frequency with which the pressure fluctuations are decreased and the volume of air ventilated is increased following the use of these drugs. These changes may be found even though patients have had continuing diffficulty despite a full therapeutic program and, in some instances, striking improvement was demonstrated.

The unexpected finding of an apparent change in compliance is noted and its significance is discussed. This finding adds emphasis to the necessity of using complete mechanical methods of study in evaluating drugs thought to affect the mechanical properties of the chest.

(*Synthesized at Lakeside Laboratories, Inc., Milwaukee).

ASPIRIN PREFERRED IN RHEUMATOID ARTHRITIS

Los Angeles—Aspirin is the analgesic of choice in treating rheumatoid arthritis and, combined with rest and physical therapy, still constitutes the basic approach in managing the condition, according to a panel discussion reported in *California Medicine* (82:367, 1955).

The panel consisted of Drs. Ephraim P. Engleman, Howard J. Weinberger, Carlos F. Sacasa, Nathan E. Headley, Roland Davison, Stacy R. Mettier and Frederic W. Rhinelander.

Aspirin not only has proven analgesic activity in rheumatoid arthritis but "has a definite effect on the connective tissues involved in the disease," Dr. Davison stated. Urging liberal use of aspirin, he recommended a dose of 15 grains every four hours during the day.

Various combinations of salicylates and other drugs, notably para-aminobenzoic acid, have failed to demonstrate any greater effectiveness than aspirin, the panel agreed. Dr. Engleman noted that "the combinations are much more expensive and, generally speaking, aspirin fills the bill very well."

The panel also concurred in preferring a conservative program of treatment, including aspirin, rest and physiotherapy, in the early stages of the disease. Steroid drugs should not be administered until it is determined that the condition is progressive, the doctors agreed. The danger of severe reactions, plus expense to the patient, were the reasons advanced by most of the panel for withholding steroid drugs whenever possible.

ANNOUNCEMENT

Dr. George H. Schneller has been appointed Director of the Project Coordination Division of the Research and Development Department of Wyeth Laboratories it was announced today by H. W. Blades, Executive Vice President.

Dr. Schneller will assist in coordinating and expediting the activities associated with the development of new or improved Wyeth pharmaceutical products. He was formerly associated with the Fine Chemicals Division, American Cyanamid Company, as Director, Pharmaceutical Applications.

Dr. Schneller received his B.S. degree from St. John's University, his M.S. from New York University and in 1947 his Ph.D. from the Polytechnic Institute of Brooklyn.

Widely-known in professional pharmaceutical circles, Dr. Schneller is a member of the American Chemical Society, the American Pharmaceutical Association and the New York Academy of Science. He is also a fellow of the American Institute of Chemists.

He is the author of numerous scientific and technical papers.

FURADANTIN

Furadantin (Eaton) has proved to be "one of the most effective single agents available at this time" for the treatment, without hospitalization, of stubborn urinary tract infections, report R. S. Breakey, M.D., S. H. Holt, M.D., and D. Siegel, M.D., in *North Central Section, American Urological Association Proceedings,* Oct. 7-9, 1954, p. 5. Of 46 cases treated with Furadantin in private practice, 20 were cured bacteriologically and 22 others were improved symptomatically but with positive culture.

Of 31 non-surgical cases, 27 were symptomatically improved: 16 were cured bacteriologically and 11 showed microscopic improvement with positive culture. All 15 surgical cases treated post-operatively with Furadantin experienced improvement: 4 were completely cured and 11 showed improved microscopic findings with positive culture. The investigators note that "all had pre-existing infection and if the follow-up had been longer, a larger number of infections might have been cured."

They further state: "Since the Pseudomonas organism which is usually extremely resistant to all forms of therapy, was eradicated in 50 per cent of our cases, we feel that Furadantin deserves a trial when this organism is found."

RECENT CORTICOSTEROID RESEARCH POINTS TO SAFE HORMONE CONTROL OF RHEUMATOID ARTHRITIS

Therapeutic implications inherent in current research efforts to find synthetic cortisone derivatives capable of controlling the various forms of arthritis without incurring undesirable corticosteroid activity were reviewed at the 19th Annual Meeting of the American Rheumatism Association in Atlantic City in June. Research scientists and medical authorities in this field of investigation presented forty papers during the eight scientific sessions of the meeting.

Some 800 delegates to the two-day meeting heard a panel of five leading investigators concur in the opinion that with the more recent corticosteroids, particularly Meticorten, the newest agent in this field of discovery, research was moving in the right direction and will find the solution to the problem of safe hormone control of arthritis.

Dr. Joseph J. Bunim, director of clinical research at the National Institute for Arthritis and Metabolic Diseases and the first to use and report on the value of Meticorten in rheumatoid arthritis, was moderator of the panel. Other members of the panel were Dr. Edward W. Boland, president of the American Rheumatism Association; Dr. Ralph E. Peterson of the National Institute of Arthritis and Metabolic Diseases; Dr. Josef Fried of New Brunswick, New Jersey; Dr. Charles H. Slocumb of Rochester, Minnesota; and Dr. Ralph I. Dorfman of Shrewsbury, Massachusetts.

Dr. Boland reported "prompt and striking antirheumatic effects" in each of 52 rheumatoid arthritis patients treated with Meticorten. The improvement pattern was similar to that obtained with larger suppressive doses of hydrocortisone and cortisone.

Subjective relief began three to seventy-two hours after institution of therapy; objective improvement was observed within two to seven days. Adequate control was obtained within seven to twenty-one days and major improvement was maintained for three to five months.

In a large percentage of 29 patients transferred to Meticorten after inadequate control with hydrocortisone, major improvement was restored with smaller doses of the new corticosteroid, according to Dr. Boland.

Comparatively small doses of 9 alpha fluorohydrocortisone administered daily to rheumatoid patients for 12 to 28 days, Dr. Slocumb declared, lessened rheumatic symptoms but troublesome retention of sodium and fluid as well as loss of potassium occurred.

Meticorten administered daily for as long as twenty-four days lessened rheumatic symptoms in these patients without significant excessive sodium retention or potassium loss. However, patients were in negative nitrogen balance.

Discussing efforts being made to increase the antirheumatic activity and to minimize the undesirable effects of cortisone and hydrocortisone by modifying the molecular structure of these hormones, Dr. Fried declared, "demonstration that specific chemical groupings can cause enhancement of antiinflammatory and reduction of salt-retaining action points to more potent and less toxic antirheumatic drugs in the future. Meticorten appears to be the first step in that direction."

ASPIRIN CALLED VALUABLE IN IDIOPATHIC PERICARDITIS

NEW YORK — Aspirin sometimes has a beneficial and even dramatic effect in the treatment of idiopathic pericarditis, according to a study by Dr. William Dressler in the *American Journal of Medicine* (April 1955).

Reporting on 42 episodes of the condition in 12 patients, he states that the outstanding clinical features are pain and fever. Aspirin's therapeutic value in some cases, plus other aspects observed in idiopathic pericarditis, suggest rheumatic activity is linked to the etiology of the condition, the author says.

The course of the disease was unaffected by sulfonamides, penicillin and streptomycin. Reports in the literature contain conflicting reports concerning the value of certain broadspectrum antibiotics. Cortisone has effected improvement, Dr. Dressler notes.

Referring to several cases "surprisingly" helped by aspirin, he cites one patient in "excruciating pain who failed to respond to hypodermic administration of Demerol." The pain was "promptly relieved by ten grains of aspirin and the patient was able to go back to work when the same dose of aspirin was repeated every four hours."

Fever persisted in another patient for five weeks despite intensive treatment with antibiotics. Aspirin was given on the 36th hospital day, Dr. Dressler says, and caused "a rapid fall of the temperature to normal."

COMPREHENSIVE STUDY OF MERCURIAL MEDICATION IN CARDIAC CASES REPORTED BY LEFF, NUSSBAUM INCLUDES BOTH CLINICAL AND LAB EVIDENCE

Report in Form Of Exhibit Is Made At A. M. A. Convention; Chlormerodrin Effective Without Renal Toxicity, and Pathologic Studies Show No Tissue Damage

"Is there accumulation of mercury in the course of treatment with mercurial diuretics?

"Is renal function impaired or damaged?

"How much mercury does accumulate in the kidney and other vital organs after extensive use of mercurial diuretics?"

Organomercurial medication in heart failure has been studied comprehensively over a long period for laboratory evidence of its effect on organs as well as its clinical effectiveness, by William A. Leff, M.D., and Harvey E. Nussbaum, M.D., cardiologists of the St. Barnabas Hospital in Newark, N. J.

The battery of tests included urinalysis, urea nitrogen, NPN, creatinine, P.S.P. tests, urea clearance tests, and electrolyte studies. There were three deaths in this series, none of whom died in failure, and autopsy studies were made in these cases.

The investigators have reported their findings in an exhibit at the convention of the American Medical Association. They are also preparing an extended report on the investigation for publication. It will describe many interesting case studies and the physiology of diuretics.

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They have found the oral organomercurial diuretic chlormerodrin (Neohydrin-Lakeside Laboratories) clinically effective without evidence of renal toxicity.

Moreover, the pathologic studies have shown no damage to the liver and kidneys, even in patients who received tremendous amounts of mercury.

Fifty patients with various heart conditions, most of them Grade III (functional capacity) or worse, had previously been given injections once or twice a week for one to eight years. In this study, they were treated with chlormerodrin and followed for periods of up to three years.

"Excellent diuretic control without injections was obtained in 45 of 50 patients," Dr. Leff and Dr. Nussbaum report. The other five required occasional booster injections. Waterlogging and the "see-saw effect of edema and dehydration produced by intermittent diureses" were avoided.

The confidence of patients improved markedly, with an increased feeling of security on their jobs.

The size of the congested liver was progressively diminished, Dr. Leff and Dr. Nussbaum point out.

Prolonged administration of mercury as chlormerodrin produced no disturbance of sodium or potassium balance, renal impairment, or alteration of renal function.

A feature of the exhibit is a chart showing that five patients, each of whom had received the equivalent of more than 30,000 milligrams of organic mercury, showed no clinical or laboratory signs of kidney damage.

In patients who died in the course of the study, pathologic followup confirmed the complete absence of change in body organs due to the organomercurial diuretics. "Microscopic examination of kidneys and livers gave no evidence of glomerular, renal, tubular or hepatic pathology attributable to mercury," it is reported. Colored photomicrographic transparencies are included in the exhibit.

"A three-year follow-up is a relatively short time in the life of a cardiac patient, and further study must be carried on," the physicians stated. "We can conclude, however, that after three years of careful clinical observation aided with laboratory tests of kidney function, histopathology, and mercurial analysis of tissues, not a single patient showed evidence of renal toxicity or impairment of renal function."

HEXACHLOROPHENE

Sindar Corporation, New York, is pleased to announce that hexachlorophene - G-11® - and hexachlorophene liquid soap have been listed in the fifteenth revision of the Pharmacopoeia of the United States.

As the discoverer and producer of G-11® (hexachlorophene), we welcome this further recognition by the medical profession and the privilege of joining the U. S. P. list of best-known and most important medical aids.

Hexachlorophene liquid soap is the only antiseptic soap recognized by the U. S. P.

NEW ANALGESIC-ANTACID PRODUCT MARKETED BY AMERICAN FERMENT

A new buffered analgesic compound tablet has been marketed by American Ferment Co., Inc.

Called Falgos Tablets, the new product is being made available through the medical and dental professions through the usual trade distribution channels. To help introduce it as "the first of its kind," a promotional campaign has started via advertising in professional journals, and is being supported by a program of direct mail, detailing and sampling.

The new compound is indicated for the relief of pain in headache, neuralgia, neuritis, muscular aches, the common cold, and following dental procedures and extractions. It is effective also in treating the minor pains of rheumatism and arthritis.

Falgos is supplied by American Ferment Co. in bottles of 15 and 40 tablets.

PANTHO-F CREAM

DESCRIPTION: 1% hydrocortisone in a stainless, white, stable, watermiscible, cosmetically pleasant cream containing 2% pantothenylol (Panthoderm Cream).

ACTION AND USES: Allays inflammation; relieves pain, itch and swelling; checks oozing and edema; reduces crusting and scaling; promotes rapid granulation and healing in: eczemas (infantile, housewives', etc.), dermatitis (atopic, contact, eczematoid), neurodermatitis, pruritus ani et vulvae, lichen chronisus simplex, in all skin conditions requiring antiinflammatory, antipruritic, healing therapy. Non-irritant, rarely sensitizes. Easily applied and removed without disturbing epithelization.

APPLICATION: Clean affected area, then gently rub in a small amount of Pantho-F Cream 2 or 3 times daily or as required. Frequency of use may be reduced as improvement is noted. When inflammation subsides treatment may be continued with Panthoderm Cream.

SUPPLY: PANTHO-F Cream —Tubes of 5 and 20 Gms.

U. S. Vitamin Corp., New York 17, New York.

DEEP MUSCLE VASODILATOR (ARLIDIN) ALLEVIATES INTERMITTENT CLAUDICATION

Arlidin, a new peripheral vasodilator, proved "excellent in alleviating the intermittent claudication and nocturnal cramps," in 19 diabetic patients who did not respond to placebo, report Drs. Julius Pomeranze, Raymond J. Gadek and associates from the N. Y. Medical College, Flower-Fifth Avenue Hospitals, New York City, in the June 1955 issue of Angiology.

Arlidin fulfills these criteria as defined by the investigators: "A good peripheral vasodilator drug should increase blood flow to muscles without greatly increasing the flow of blood into skin vessels or into less sclerosed arteries. Generalized vasodilatation will cause a diminishing volume flow in the less distensile atherosclerotic peripheral vessels where it is needed. An increased cardiac output is required to compensate for relative diminution of blood volume."

Animal and human pharmacologic studies indicate Arlidin HCl. provides "strong muscle vasodilator activity and an adequate increase in cardiac output." Clinical evaluation indicates "excellent results in recovery from intermittent claudication." Patients on an oral dosage of 3 mg. to 12 mg. of Arlidin, three or four times a day, had satisfactory relief of claudication, increased walking ability (distance/time), dis-

appearance of nocturnal cramps, and, as a result, more restful slumber. Each time placebo was substituted, there was exacerbation of symptoms; each time therapy was resumed, symptoms were relieved.

A feeling of tingling and warmth was usually experienced within ten minutes of taking Arlidin. Two patients had slight dizziness and weakness, which were insufficient to discontinue therapy. No other side effects were encountered. The investigators consider Arlidin "a safe vasodilator which acts rapidly and regularly."

NUTRITION EDUCATION

Public Health Officers everywhere have the responsibility to include nutrition education as a part of a community health program is the recommendation of a new publication of the American Public Health Association.

"Nutrition Practices" describes the role of nutrition in modern public health practice. This Guide for public health administrators is the result of two years of study by a subcommittee of the Association's Committee on Administrative Practice.

Dr. Daniel Bergsma, New Jersey state health commissioner, was chairman of this committee of nutrition researchers, teachers and consultants, and of state and local health administrators. Its members were: John Browe, M.D.; Leroy E. Burney, M.D.; Alfred L. Frechette, M.D.; Grace Goldsmith, M.D.; James M. Hundley, M.D.; Frances MacKinnon; L. A. Maynard, Ph.D; Robert Shank, M.D.; Alice Smith; Helen Stacey; Fredrick J. Stare, M.D.; Helen Walsh and Carl A. Wilzbach, M.D. In addition more than 100 persons read drafts of the manuscript and contributed suggestions and ideas.

Aiding the larger committee was a small working committee of nutritionists, made up of Elizabeth Caso, Catherine M. Leamy, Isabel Patterson and Marguerite J. Queneau.

Their combined efforts have produced an authoritative guide to the administration of public health nutrition programs and for the evaluation of nutrition services.

Nutrition is an essential part of any competent public health program, says the Guide. The responsibility of public health in this field is essentially educational—the guidance of both individuals and groups. Public health shares with the medical profession and voluntary agencies responsibility for a program of preventing nutritional disorders, establishing sound eating habits, maintaining desirable weight.

Some of the questions to which the health administrator will find the answers in this Guide are:

What are the objectives of public health nutrition services?

What is the role of the public health administrator?

How does he go about utilizing opportunities to carry out his role?

How are these opportunities found?

What is the place of the nutrition program in the entire program of the health department?

How can staff members, apart from nutrition personnel, extend the nutrition program?

The premises upon which the Guide is built are:

Good nutrition is a prerequisite for good health — a fundamental fact established beyond dispute;

Though the nutrition of Americans seems better than in recent decades, demonstrable nutritional deficiencies still are found;

Obesity is a growing hazard to health;

Defective nutrition is an insidious and ever-changing challenge to public health, and

Preventive programs call for the effective working together of many agencies and the collaboration of several professional groups.

"Nutrition Practices: A Guide for Public Health Administrators," 80 pages, 13 illustrations, may be obtained from the American Public Health Association, 1790 Broadway, New York 19, N. Y., at $1.00 per single copy, 75 cents per copy in quantities of 25 or more. Cash should accompany orders for single copies.

GANTRISIN

Gantrisin Nasal Solution, a highly effective antibacterial-decongestant, has been made available for over-the-counter sale by Hoffmann-La Roche Inc.

Gantrisin Nasal Solution, indicated for local treatment of acute and chronic bacterial infections of the nose and sinuses, can be administered by dropper or atomizer into the nostrils as well as by displacement techniques.

Gantrisin Diethanolamine Nasal Solution 'Roche' is available in 30-cc bottles equipped with droppers. Druggists' list price, $1.06; fair trade minimum, $1.77.

ASTEROL

Nutley, N. J.—Asterol Powder, a broad-spectrum antifungal dusting powder available only for prescription use up to the present time, is now marketed for over-the-counter sale by Hoffmann-La Roche Inc.

The combined use of Asterol in powder, tincture, and ointment form has proven highly effective in the treatment of "athlete's foot." A primary indication for the dusting powder, however, is daily prophylactic use following subsidence of the fungus infection in order to prevent recurrence.

Asterol Tincture and Asterol Ointment will continue to bear the prescription legend.

Asterol Dihydrochloride 'Roche,' brand of diamthazole dihydrochloride, is available as a dusting powder in 1½ ounce shaker cans. Druggists' list price, $.90; fair trade minimum, $1.50.

NATIONAL FUND FOR MEDICAL EDUCATION

The National Fund for Medical Education has produced its first documentary film, "Danger at the Source," it was announced by the Fund's president, S. Sloan Colt, New York.

Prepared as a public service by Fox Movietone, the 13½ minute film tells the story of medical education in America. Ray Middleton, star of "Annie Get Your Gun" and "South Pacific," contributed the narration.

"Filmed in medical schools and teaching hospitals, supervised by leading medical educators, 'Danger at the Source' highlights the glories and the hard work of the American brand of medical teaching that has made ours the healthiest nation in the world," Colt said.

"Our first film will be a potent aid in bringing home to the American public the critical importance of the nation's 81 medical schools, the seed-bed of all medical care.

These schools face the threat of diminishing funds to carry on their teaching programs. Medical education and the need to support it as a free and progressive force for the national welfare is the business of all of us. I hope the film will make this obligation apparent to all who view it."

The National Fund for Medical Education was founded in 1949 to gain private support for the medical schools. The Fund has already distributed nearly $7 million in unrestricted grants to the 81 schools. The need—and the goal—is $10 million each year.

VITAMIN RESEARCH

Sixteen new grants to American universities and medical centers throughout the country will augment the extensive program of clinical and laboratory research in the fields of vitamins and nutrition of The National Vitamin Foundation, Inc., it was announced today by Dr. Robert S. Goodhart, Scientific Director of the Foundation for its broadened continuing program of scientific research.

The National Vitamin Foundation gives grants-in-aid for research semi-annually throughout the United States and abroad. The new grants became effective July 1, 1955, and include grants to:

Dr. William S. Alexander, St. Louis University, St. Louis, Missouri; $5,000.00 for studies of the effect of vitamin B_{12} on experimental amyloidosis, and studies of the effect of experimental amyloidosis on nerve tissues and vitamin B_{12} as a protective agent.

Dr. Walter J. Bo, University of North Dakota, Grand Forks, North Dakota; $3,100.00 for a histochemical study of uterine metaplasia in the rat following vitamin A deficiency and studies of the relationship between hypervitamin A and estrogen on uterine epithelia.

Dr. Bacon F. Chow, The Johns Hopkins University, Baltimore, Maryland; $3,000.00 for studies of vitamin B_{12} and aging.

Dr. George R. Cowgill, Yale University, New Haven, Connecticut; $4,500.00 for studies of the physiology and biochemistry of pantothenic acid deficiency.

Dr. Albert B. Eisenstein, Washington University, St. Louis, Missouri; $4,500.00 for studies of the relationship of pantothenic acid to adrenocortical hormone secretion.

Dr. George J. Gabuzda, Western Reserve University, Cleveland, Ohio; $5,000.00 for studies of the metabolism and interrelationship of folic acid, citrovorum factor and ascorbic acid.

Dr. Irving Graef, 4th Medical Division (New York University) Bellevue Hospital, New York, New York; $4,000.00 for studies of the effect of pantothenic acid deficiency in various disease states.

Dr. G. Watson James, III, Medical College of Virginia, Richmond, Virginia; $5,000.00 for studies of vitamin B_{12} growth activity of *P. stipitata* in human leukemia.

Dr. B. Connor Johnson, University of Illinois, Urbana, Illinois; $4,950.00 for studies of the role of vitamin B_{12} in animal nutrition.

Dr. Albert L. Lehninger, The Johns Hopkins University, Baltimore, Maryland; $3,050.00 for studies of the enzymatic mechanism of ascorbic acid biosynthesis in animal tissues.

Dr. Herman C. Lichstein, University of Minnesota, Minneapolis, Minnesota; $6,600.00 for studies of the use of compounds structurally related to biotin for the study of the mechanism of action of biotin.

Dr. R. W. Luecke, Michigan State College, East Lansing, Michigan; $3,000.00 for studies of the quantitative requirements of the baby pig for certain vitamins.

Dr. A. Leonard Luhby, New York, New York; $3,600.00 for studies of the evaluation of urinary formamido-L-glutamic acid excretion as a clinical test for folic acid undernutrition.

Dr. O. Neal Miller, Tulane University of Louisiana, New Orleans, Louisiana; $4,000.00 for studies on the metabolism of vitamin B_{12} in man with special reference to interactions among serum proteins, intrinsic factor and the vitamin.

Dr. Robert E. Olson, University of Pittsburgh, Pittsburgh, Pennsylvania; $6,296.00 for studies of the effect of dietary fat and choline upon the serum lipids and lipoproteins of the rat.

Dr. Theodore F. Zucker, Columbia University, New York, New York; $5,170.00 for studies of pantothenic acid deficiency and the status of acetylcholine in intestinal tissue.

PARKE-DAVIS REPORTS 'SUBSTANTIAL INCREASES' IN NET SALES, EARNINGS FOR FIRST SIX MONTHS

Parke, Davis & Company, worldwide pharmaceutical firm, today reported "substantial increases" in net sales and earnings for the first six months of 1955.

Net earnings in the first half of 1955 totalled $6,393,863, equivalent to $1.31 on each of the 4,897,961 shares of common stock outstanding. This was after deducting and reserving during that period an amount of $562,351, equivalent to 1955 local net earnings to date in Argentina. Had such earning been included, as they were in prior years, consolidated net earnings for the first half of 1955 would have been $6,956,214, equal to $1.42 a share. In the first six months of last year, net earnins amounted to $4,557,515, or 93 cents a share.

Parke-Davis reported net sales of $59,790,806 for the 1955 half-year period. This compares with $52,584,951 for the like period last year.

Harry J. Loynd, president, explained, "The substantial increase in our earnings is the result of many factors, including a continuing strong emphasis on sound cost and expense relationships, and an upward trend in sales."

The company, which has made a profit every year since 1876, had net sales of $28,805,972 and earnings of $2,832,063 in the first quarter of 1955. Second quarter figures were sales; $30,984,834, and earnings; $3,561,800.

Parke-Davis will pay its 271st consecutive dividend on July 29 to more than 25,000 stockholders of record July 8. The dividend will amount to 35 cents per share, the third such payment this year.

PFIZER OFFERS TWO COLORING AGENTS FOR FOOD INDUSTRY

Two coloring agents, Pfizer Vegetable Color and Pfizer Beta Carotene, were offered today to the food industry by Chas. Pfizer & Co., Inc., one of the world's largest manufacturers of vitamins and other special-

ty products for the food and allied industries.

Both products, which can be blended with vitamin A to specification, show a high degree of color uniformity and stability. Their use is seen ideal in imparting a natural yellow color to margarine, shortening, butter, bakery products, edible oils and allied products.

Pfizer Vegetable Color is an oil-soluble 20% suspension of microcrystalline annatto color in refined winterized cottonseed oil, according to Paul E. Weber, assistant sales manager, Chemical Sales Division, who made the announcement.

According to Weber, Pfizer Vegetable Color is very stable and highly compatible with vitamin A. The product's "excellent coloring properties," he added, are evident when blended with this essential vitamin or used alone.

Weber also noted that a series of Pfizer Vegetable Color-vitamin A compatability tests, run under margarine processing conditions, showed no loss of color or vitamin A content. In the tests, Pfizer Vegetable Color samples were added to margarine and the resultant mixture heated for six hours at 140° F.

Similarly, Weber pointed out, no loss of color or vitamin A was detected in these margarine samples after storage for 20 weeks at room temperature.

Pfizer Beta Carotene is a stable, nutritional coloring agent with high vitamin A activity, Weber said. Easy to handle, it can be blended with additional vitamin A for full nutritional value, he added.

The provitamin A content of beta carotene is converted into vitamin A in the body. It is a natural coloring matter in carrots, sweet potatoes, many leafy vegetables, butter, milk fat and other dairy products.

Both Pfizer Vegetable Color or Beta Carotene are available in bulk or in custom blends with vitamin A from Pfizer's Brooklyn, N.Y., and Groton, Conn., plants.

Additional information on the two coloring agents is obtainable from the company's Chemical Sales Division, 630 Flushing Avenue, Brooklyn 6, New York.

MEDICAL BOOK GUILD

The August selection of the Medical Book Guild of America is PSYCHIATRY FOR THE FAMILY PHYSICIAN by C. Knight Aldrich, M. D., Associate Professor of Psychiatry, University of Minnesota Medical School. Presenting emotional factors in illness, emotional illnesses, and psychopathological states as the family doctor encounters them, it provides an initial background in psychodynamics and psychiatric principles which will be helpful to the physician in the context of his everyday practice. The final section on diagnosis and treatment covers methods which the family physician can adopt to his own use.

BLACK EYES

Rapid healing of black eyes following tiny injections of the enzyme trypsin, first guardedly reported last summer, is standing the test of time, it is reported here.

Drs. Joseph M. Hopen and Francis N. Campagna of Philadelphia General Hospital reported in their hospital journal a year ago that five cases of badly swollen black eyes had responded quickly to trypsin therapy, and announced their intention to conduct further clinical tests.

In the current (July) issue of the American Journal of Ophthalmology the two ophthalmologists report that their experience now encompasses 20 black eye cases. The same excellent results—reduction of pain, swelling and inflammation in one or two days, rather than a week or so—were obtained in 16 cases. There was no reduction of discoloration.

In the other four, the doctors report "equivocal" or questionable results, indicating that the patients might have done as well under conventional therapy. In no case did they report untoward results, and they call the enzyme safe and effective in ocular conditions characterized by inflammatory reactions.

In about 30 percent of cases, patients complain of pain in the buttock where the enzyme is injected, but no toxic reactions were observed, according to the report.

Encouraged by the dramatic action of trypsin in reversing inflammation and swelling, Drs. Hopen and Campagna tested it in a wide variety of eye disorders having those characteristics. In some they got excellent results, while in others the enzyme produced little effect.

In diabetic retinitis, for example, a rupture of eye veins in victims of diabetes, where success was not expected, the first patient reacted favorably. But in 17 additional patients, there was no improvement, and the original success relapsed.

The eye specialists thus conclude that trypsin therapy probably has no value in treating diabetic retinitis. Similarly, in hemorrhages of the retina, they had three test cases, and can reach no conclusion without further study.

But in six cases of inflammation of the uveal tract, all cleared up; some rapidly and one after 49 days of treatment. In single cases of acute retrobulbar neuritis and acute dacryocystitis, similar success was obtained.

In all, Drs. Campagna and Hopen report on 63 patients in their current paper. Postoperative hyphema (hemorrhage in the eye's front chamber) cleared in five out of six cases, but in ethmoiditis and endophthalmitis (inflammation in the eye socket and interior structures, respectively), no improvement due to trypsin therapy was noted.

Vitreous hemorrhages may react well to trypsin if caught early. One of a single day's standing cleared completely, while older ones reacted less favorably, with no change noted in those of a year or more duration.

The trypsin preparation used by the two doctors is called Parenzyme, and is made by Philadelphia's National Drug Company. Only tiny injections are given—about an 11,000th of an ounce of the enzyme suspended in about a 60th of an ounce of sesame oil.

Queried about future plans for using Parenzyme, Dr. Campagna noted that the outward evaluation of 32 successes, even doubtful cases and 25 failures was "encouraging for a study of this type."

By eliminating the 18 cases of diabetic retinitis, in which ineffectiveness of the enzyme was apparently confirmed, a success rate of 71 percent good and 15 percent doubtful is established, against failures of only 14 percent, he pointed out.

And in conditions helped by trypsin therapy, the success rates run 80 percent or better, he added.

USE OF INTRAMUSCULAR TRYPSIN IN TRAUMATIC INFLAMMATORY AND HEMORRHAGIC OCULAR DISTURBANCES

JOSEPH M. HOPEN, M. D.*
AND
FRANCIS N. CAMPAGNA, M. D.**

HISTORICAL

In 1932 John H. Northrop (1) and his colleagues at the Rockefeller Institute for Medical Research succeeded in isolating trypsin as a purified crystalline material.

In 1950 Reiser and his associates (2) used solutions of trypsin by injection into closed cavities to lyse viscous exudates. It was also used by inhalation to liquefy tenacious mucus (3).

In 1952, Imerfield et al (4) postulated that enzymatically induced anticoagulation, thrombolysis and fibrinolysis followed intravenous administration of purified crystalline trypsin. Subsequent clinical studies (5, 6, 7, 8), based on the use of trypsin in more than one thousand patients, gave evidence that trypsin rapidly suppressed acute inflammations of diversified origin, bacterial, viral, allergic, or chemical.

INTRODUCTION

In 1953, Hopen (9, 10) reported an attempt to utilize the known proteolytic and anti-inflammatory properties of trypsin by using the drug intravenously in acute inflammatory and hemorrhagic ocular disturbances. It was observed that in a large percentage of the cortisone-resistant ocular cases, seventy-nine per cent, a prompt and sustained suppression of the acute inflammation resulted.

However, following reports from several other investigators (11, 12), it was apparent that the intravenous use of trypsin was not an innocuous procedure.

In March, 1954, Hopen and Campana (13) administered crystalline trypsin in sesame oil* deep intramuscularly in a series of diversified ocular conditions. The anti-inflammatory and thrombolytic effects of the intramuscular trypsin were apparent in the clinical conditions comprising this investigation. The results of this preliminary report encouraged these investigators to pursue a further exhaustive study on the use of trypsin in ophthalmologic pathology.

This study encompasses 63 patients representing 8 ocular pathologic entities in which inflammation, edema and pain were dominant complication factors as presented in Table I.

PROCEDURE OF TREATMENT

Dosage: The initial course of treatment consisted of 2.5 mgm. of trypsin in sesame oil (0.5 cc.) injected deep intragluteally, using a dry sterile syringe, every 8 hours for the first 48 hours, then every 12 hours for 4 days. The duration of treatment depended on the course of the disease; some patients required only six or seven injections.

Maintenance therapy: In chronic or recurrent ocular diseases, 2.5 mgm. (0.5 cc.) of the trypsin in oil once or twice per week for several weeks frequently resulted in maximum satisfactory benefit.

CLINICAL RESULTS

The distribution of the 63 patients according to ocular pathology, and the results in each category, are as follows:

1. EXTRAOCULAR TRAUMA (20 cases)

Of the 20 extraocular trauma cases treated with trypsin in sesame oil, 16 had a very good response. Pain and swelling decreased in 48 hours or less. In 4 cases the results were equivocal.

SELECTED CASE REPORT

I. B., a 27-year-old colored female, was struck with a fist in the left eye. The eye remained swollen seven days prior to seeking medical attention in the Eye Clinic. The patient was started immediately on intramuscular trypsin in sesame oil. After 24 hours there was noted subjective diminution of pain and marked objective decrease in swelling of the eyelids. Forty-eight hours later the eye was completely open. The patient showed only a slight residual subconjunctival hemorrhage remaining in the traumatized eye. The patient was discharged on the sixth day with the ocular condition completely resorbed.

2. HYPHEMA (POST-OPERATIVE) (6 cases)

All six cases in this group had anterior chamber hemorrhage following cataract extractions. Treatment with trypsin produced a decrease in the hemorrhage within 24 to 48 hours in 5 of the 6 cases. Four cases were completely cleared in 72 hours, the fifth cleared in five days. There was one failure in this group.

SELECTED CASE REPORTS

W. P., a 52-year-old colored female, diabetic, had a senile cataract removed from the right eye. A large anterior chamber hemorrhage was noted at the first dressing. Intramuscular trypsin was given, 2.5 mgm. (0.5 cc.) each 8 hours; after 24 hours the hemorrhage showed evidence of decreasing. At 72 hours it was completely absorbed.

3. UVEAL TRACT INFLAMMATION (6 cases)

Five of the six cases showed some improvement in one week or less. Of two cases which took the longest time to clear, one required 6 weeks and the second 7 weeks to return to normal. All cases cleared.

SELECTED CASE REPORTS

W. R. S., a white male, member of the medical profession, had uveitis since 1938 when it lasted one month, again in 1945 for 6 weeks, 1951, for one month, and 1953 for 11 months up to time of present treatment. Complete fogging of vision of left eye on awakening. Vision 20/400 on February 19, 1954, continued 20/400 to September 11, 1954, when trypsin in oil via the intramuscular route was started—2.5 mgm. (0.5 cc) twice daily. On September 15, vision was 20/50 and trypsin was given once daily. On October 7, 1954, patient developed severe generalized urticaria 15 minutes following trypsin injection. Treatment discontinued. Vision has remained 20/50 at last examination, Novem- 1, 1954, and patient is grateful for the marked improvement.

4. RETINAL HEMORRHAGE (3 cases)

The results in these three cases were equivocal—many more cases are necessary for positive evaluation.

5. VITREOUS HEMORRHAGE (5 cases)

Of the 5 cases in this group, only two showed definite improvement which could be credited to the trypsin in sesame oil treatment. One case cleared completely in 8 weeks and the other was partially cleared after 4 weeks. Two patients with chronic vitreous hemorrhage (one year and several years' duration)

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*Parenzyme: Medical Research Department. The National Drug Company, Philadelphia 44, Pa.

manifested no change in their conditions.

SELECTED CASE REPORTS

C. P., a 73-year-old colored female, diabetic, was referred by a former Resident Physician with a diagnosis of massive vitreous hemorrhage, right eye, of one day duration. Fundus view of right eye not possible because of vitreal hemhorrhage. Left eye aphakic, fundus normal. Visual acuity was light perception in right eye, 6/15 in left eye with correction. Patient started on intramuscular trypsin, 2.5 mgm. (0.5 cc.) twice daily. One week later patient saw 6/60 in right eye. Fundus examination of right eye now possible—showed a resorbing hemorrhage in vitreous. Trypsin treatment continued another week —at which time the patient's vision was 6/15 and further clearing of the vitreous was noted. Vision continued to improve so that on 8 weeks of treatment visual acuity in the right eye was 6/12+4 (same as previous best acuity) and there was no evidence of previous hemorrhage in the vitreous. The patient has been followed for 6 months and maintained on one injection (2.5 mgm.) of trypsin in oil at weekly intervals. No recurrence of hemorrhage has been observed to this time.

6. SECONDARY INFLAMMATION
(3 cases)

Two of the cases had acute retrobulbar neuritis and acute dacryocystitis, and had good results on trypsin in sesame oil treatment. The third case, with proptosis secondary to ethmoiditis, did not improve surgical drainage was instituted.

7. DIABETIC RETINAL HEMORRHAGE

A. G., a 57-year-old colored female, diabetic, seen in Eye Clinic with complaint of sudden dimness of vision in right eye. Fundus showed a retinitis in both eyes with what appeared to be fresh hemorrhage in right eye. Visual acuity was 3/60 right eye and 6/60 left eye. Trypsin in oil, 2.5 mgm., was given intramuscularly twice daily for two weeks with little improvement, and was continued for three more weeks. Acuity improved to 6/30 in right eye at this time, but funduscopically little improvement was noted.

8. DIABETIC RETINITIS
(18 cases)

Since one case of acute retinal hemorrhoge in a diabetic patient apparently cleared following trypsin therapy (13), the treatment was used in an attempt to clear old hemorrhages in diabetic patients.

There was no apparent change in the appearance of the fundi and no improvement in visual acuity in all 18 patients in this series.

9. INTRAOCULAR INFECTIONS

These were cases of endophthalmitis in which trypsin was used as an adjunct to antibiotic therapy. No improvement resulted and in both cases the eye had to be enucleated.

SELECTED CASE REPORT:

E. V., a 60-year-old white female, was admitted with a diagnosis of bullous keratitis right eye and secondary endophthalmitis. She was immediately given large doses

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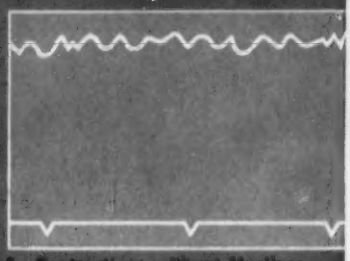

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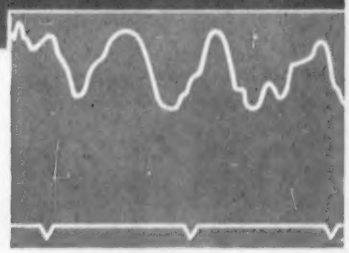

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of antibiotics systemically and by topical application chloramphenicol. Trypsin in oil was started simultaneously, since the globe was exquisitely tender. There was subwas immediately given large doses jective improvement within 48 hours; however, objectively, the eye was unchanged. After 12 days trypsin therapy had to be interrupted because the patient complained of severe pain following injection into the buttocks. Two days later a large hypopyon developed in the right eye, and the eye had to be enucleated soon thereafter.

10. MACULAR HEMORRHAGE

J. H., a 30-year-old colored male, was struck in the right eye 3 days prior to admission. Fundus examination of right eye showed a large hemorrhage in the macular area. Trypsin in oil was given intramuscularly, 2.5 mgm. twice daily. The hemorrhage cleared very gradually without return to normal function. The patient was discharged after 7 weeks with large central scotoma.

CONTRAINDICATIONS:

Trypsin, either intravenous or intramuscular, should be used with caution in patients with blood clotting abnormalities, impaired liver or renal function, acute pancreatitis or with hemorrhage states. The drug should not be used in patients with known sensitivity to parenterally injected oil.

SIDE EFFECTS:

No toxic reactions have been reported, nor have we observed any, following the use of intramuscular trypsin. In our experiences, 30 per cent of the patients complained of pain at the site of injection, and in two patients it was severe enough to necessitate interruption of trypsin therapy. One patient experienced a generalized urticaria after the fourth day of treatment; treatment was stopped.

Since intramuscular trypsin acts only to reduce inflammation and seems to promote reparative processes, it should not be used as a substitute, but rather as an adjunct to antibiotic therapy in the treatment of acute infection with marked inflammation.

DISCUSSION:

The mechanism of the action of intramuscular trypsin in modifying inflammation, edema, and alleviating pain has not been elucidated. It has been suggested that the trypsin activates a system of naturally occurring enzymes (14). In small intramuscular doses, trypsin may function to re-establish or accelerate biological continuity and to activate anti-inflammatory mechanisms (6, 7, 8). Whatever the mechanism, clinical experiences attest to the effectiveness of trypsin in oil in the treatment of extraocular trauma, uveal tract inflammation, and in anterior and in some posterior chamber hemorrhages. Chronic ocular conditions such as intraocular infections, retinal hemorrhages and diabetic retinitis were not responsive to this type of therapy.

SUMMARY

1. The historical background for pure crystalline trypsin is reviewed.
2. The use of trypsin in ocular diseases is reviewed.
3. Procedure and treatment is outlined.
4. Of 20 cases of extraocular trauma, 16 had a very good response, and in 4 cases the results were equivocal.
5. Of 6 coses of hyphema (postoperative), 5 cases were benefitted and one case was a failure.
6. Of 6 cases of uveal inflammation, all cases cleared—4 cases within 2 weeks, 1 case in 6 weeks anl 1 in 7 weeks.
7. Retinal hemorrhages observed in 3 cases gave equivocal results.
8. Of 5 cases of vitreous hemorrhage, only two showed definite improvement. There was no change at all in 2 chronic cases.
9. Of 3 cases of secondary inflammation, 2 cases of dacryocystitis had gratifying results; one case of proptosis secondary to ethmoiditis improved following surgical drainage.
10. There was therapeutic failure in all 18 cases of diabetic retinitis.
11. Failure resulted in 2 cases of endophthalmitis; both cases had to submit to enucleation of affected eye.
12. No toxic effects were observed; some pain at site of injection in about 30 per cent of the cases.
13. One case of generalized urticaria occurred in the course of this study. May have been coincidental.

CONCLUSIONS:

Clinical experiences with trypsin in sesame oil attest the safety and effectiveness of this enzyme in those ocular conditions characterized by inflammatory reactions. Edema and acute inflammation readily respond to this therapeutic agent and pain is rapidly and effectively alleviated.

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The RESIONS act by ion exchange . . . to attract, bind and remove toxic materials in diarrheas caused by food or bacterial toxins, by prolonged use of certain drugs, and in general infectious diseases.

The RESIONS *are safe* because they are totally insoluble and non-toxic.

RESION therapy will control about 90% of common diarrheas.

RESION P-M-S is intended specifically for rapid control of those rare diarrheas caused by Gram-negative organisms; to prevent secondary bacterial infection; in mycotic diarrhea following the use of the broad-spectrum antibiotics, and to inhibit the enteric growth of *C. albicans* (Monilia).

Resion

time-tested, adsorbent effectiveness

Polyamine methylene resin	10%
Sodium aluminum silicate	10%
Magnesium aluminum silicate	1.25%

CONGO MAGIC
(Dysentery Fetish)
RESION therapy now works scientific magic against diarrhea.

and

Resion P-M-S

A new formula providing antibacterials to combat bacillary and fungal vectors

NATIONAL

Each 15 cc. contains the RESION formula plus:

Polymyxin-B sulfate	125,000 units
Phthalysulfacetamide	1.0 Gm.
Para hydroxybenzoic acid esters	0.235 Gm.

Dosage: **RESION—1 tablespoonful hourly for 4 doses; then every 3 hours while awake. RESION P-M-S—1 tablespoonful hourly for 3 doses; then 3 times daily.**

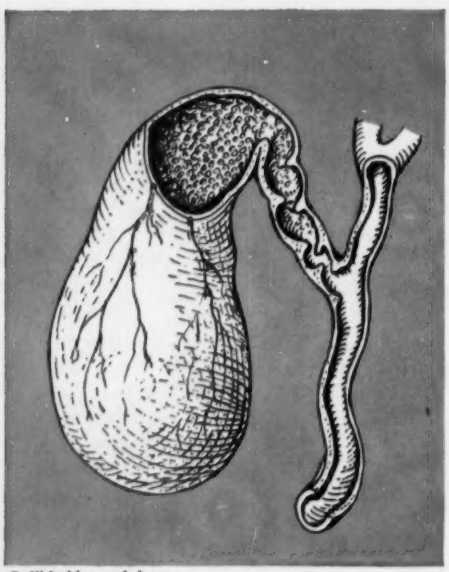
Supplied: **RESION, in bottles of 4 and 12 fluid ounces. RESION P-M-S, bottles of 4 fl. oz.**

THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.

KETOCHOL® IN GALLBLADDER DISEASE

By increasing bile secretion with Ketochol and controlling sphincter of Oddi spasticity with Pavatrine®, a free flow of bile is instituted with resultant symptomatic improvement.

Conservative, Effective Medical Management



Gallbladder and ducts.

The ketocholanic acids in Ketochol stimulate the flow of hepatic bile and flush the bile ducts. Antispasmodic medication, as provided in Pavatrine, diminishes gastrointestinal irritability and, by relaxing the sphincter of Oddi, effectively reduces symptoms of colic. This therapeutic program offers rational, conservative therapy in gallbladder dysfunction.

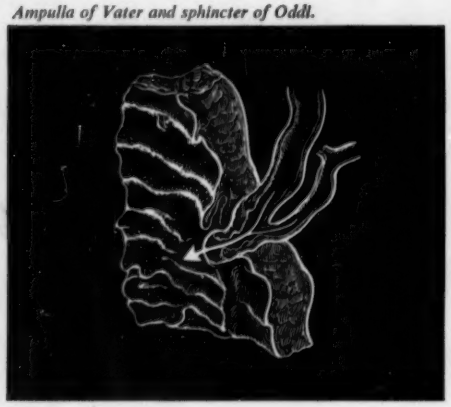
That the four bile acids present in Ketochol relieve biliary stasis is even more definitely proved by their use in the diagnosis of nonvisualized gallbladders. After the administration of Ketochol, repeat cholecystograms permitted[1] correct diagnoses.

In conjunction with the foregoing medication, proper diet, adjusted intake of milk and cream and mental relaxation are important.

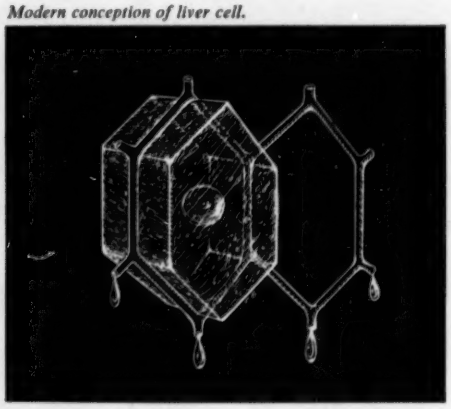
The average dose of Ketochol is one tablet three times daily with or following meals. The average dose of Pavatrine or Pavatrine with Phenobarbital is one or two tablets three or four times daily as needed. G. D. Searle & Co., Research in the Service of Medicine.

1. Berg, A. M., and Hamilton, J. E.: A Method to Improve Roentgen Diagnosis of Biliary Diseases with Bile Acids, Surgery *32*:948 (Dec.) 1952.

Ampulla of Vater and sphincter of Oddi.



Modern conception of liver cell.



SEARLE